Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US04/041069

International filing date: 10 December 2004 (10.12.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/528,184
Filing date: 10 December 2003 (10.12.2003)

Date of receipt at the International Bureau: 17 January 2005 (17.01.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

1269968

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

January 06, 2005

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *60/528,184*
FILING DATE: *December 10, 2003*
RELATED PCT APPLICATION NUMBER: *PCT/US04/41069*

UNITED STATES PATENT AND TRADEMARK OFFICE
DEPARTMENT OF COMMERCE

Certified By

Jon W Dudas

Under Secretary
of Commerce for Intellectual Property
and Acting Director of the
Unites States Patent and Trademark Office

PTO/SB/16 (08-03)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.

INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
David S.	Garvey	Dover, MA

Additional inventors are being named on the 0 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Nitrosated and/or Nitrosylated Pyruvate Compounds, Compositions and Methods of Use

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☑ Customer Number: 25270

OR

☐ Firm or Individual Name	Edward D. Grieff				
Address	Hale and Dorr LLP				
Address	1455 Pennsylvania Avenue, NW				
City	Washington	State	DC	Zip	20004
Country	US	Telephone		Fax	202-942-8484

ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 54
☐ CD(s), Number
☐ Drawing(s) *Number of Sheets*
☑ Other (specify) Return Postcard
☐ Application Date Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☑ Applicant claims small entity status. See 37 CFR 1.27.
☐ A check or money order is enclosed to cover the filing fees.
☑ The Director is herby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 08-0219
☐ Payment by credit card. Form PTO-2038 is attached.

FILING FEE Amount ($): $80.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☑ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE

TYPED or PRINTED NAME Edward D. Grieff

TELEPHONE 202-942-8400

Date December 10, 2003

REGISTRATION NO. 38,898 *(if appropriate)*

Docket Number: 102258.368

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

NITROSATED AND/OR NITROSYLATED PYRUVATE COMPOUNDS, COMPOSITIONS AND METHODS OF USE

FIELD OF THE INVENTION

The invention describes novel nitrosated and/or nitrosylated pyruvate compounds and pharmaceutically acceptable salts thereof.

BACKGROUND OF THE INVENTION

Normal metabolic processes in vascular cells are associated with the generation of reactive oxygen intermediates that must be neutralized in order to limit oxidative damage and cellular dysfunction. In the setting of common disorders or in the presence of common risk factors for numerous diseases reactive oxygen species (ROS) are generated in abundance, and their rate of synthesis and flux typically exceeds the capacity of endogenous antioxidant mechanisms. For example, hypercholesterolemia, hyperglycemia (Keaney et al, *Circulation*, 99:189-191 (1999)), cigarette smoking, hyperhomocysteinemia, hypertension, and atherosclerosis are all accompanied by an increase in plasma and tissue ROS generation. Superoxide anion, hydrogen peroxide, hydroxyl radical, peroxynitrite, and lipid peroxides all increase in diseases resulting from oxidative stress.

It is believed that oxidative damage is mediated by intracellular redox-active metal reactions catalyzed by highly reactive oxygen species (i.e. hydroxyl radicals). The generation of such reactive oxygen species depends on the availability of their common precursor, the superoxide anion. Mitochondria, microsomes and other various enzyme systems are known to produce superoxide anion that reacts with nitric oxide at or near diffusion controlled rates to form the powerful oxidant peroxynitrite. At pH 7.4, peroxynitrite protonates to form peroxynitrous acid (pKa 6.6) which decays homolytically to form hydroxyl and nitrogen dioxide radicals in addition to a host of other ions. The extent to which these later reactive ions and radicals can cause cellular damage and death depends on the rate of formation of their peroxynitrite precursor. The invention is directed to these, as well as other, important ends.

SUMMARY OF THE INVENTION

The invention provides novel pyruvate compounds that are substituted with at least one NO_2 and/or NO group (i.e., nitrosated and/or nitrosylated), and pharmaceutically acceptable salts thereof. The pyruvate compound can be nitrosated and/or nitrosylated through one or more sites

such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation) and/or nitrogen. The invention also provides compositions comprising the novel compounds described herein in a pharmaceutically acceptable carrier.

The invention is also based on the discovery that administering at least one pyruvate compound or pharmaceutically acceptable salts thereof, that is optionally substituted with at least one NO_2 and/or NO group (i.e., nitrosated and/or nitrosylated), and, optionally, at least one nitric oxide donor can be used for the delivery of nitric oxide at the targeted site. Nitric oxide donors include, for example, S-nitrosothiols, nitrites, nitrates, N-oxo-N-nitrosamines, SPM 3672, SPM 5185, SPM 5186 and analogues thereof, and substrates of the various isozymes of nitric oxide synthase. Thus, another embodiment of the invention provides compositions comprising at least one pyruvate compound that is optionally substituted with at least one NO_2 and/or NO group (i.e., nitrosated and/or nitrosylated), and at least one compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium (NO^+) or nitroxyl (NO-), or as the neutral species, nitric oxide (NO•), and/or stimulates endogenous production of nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase. The invention also provides for such compositions in a pharmaceutically acceptable carrier.

Yet another embodiment of the invention provides compositions comprising at least one pyruvate compound, that is optionally substituted with at least one NO_2 and/or NO group (i.e., nitrosated and/or nitrosylated), and, optionally, at least one compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium (NO^+) or nitroxyl (NO-), or as the neutral species, nitric oxide (NO•), and/or is a substrate for nitric oxide synthase and/or at least one therapeutic agent, including, but not limited to, aldosterone antagonists, alpha-adrenergic receptor antagonists, antidiabetic compounds, anti-hyperlipidemic drugs, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antioxidants, antithrombotic and vasodilator drugs, beta-adrenergic blockers, calcium channel blockers, diuretics, endothelin antagonists, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and mixtures of two or more thereof. The invention also provides for such compositions in a pharmaceutically acceptable carrier.

Yet another embodiment of the invention provides methods for the treatment of diseases resulting from oxidative stress, diabetes, reperfusion injury following ischemia, preservation of tissues, organs, organ parts and/or limbs comprising administering to the patient a therapeutically effective amount of at least one pyruvate compound, that is optionally substituted with at least one NO_2 and/or NO group (i.e., nitrosated and/or nitrosylated), and, optionally, at least one compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium (NO^+) or nitroxyl (NO-), or as the neutral species, nitric oxide (NO•), and/or stimulates endogenous production of nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase (i.e. NO donor). The methods can optionally further comprise the administration of at least one therapeutic agent, such as, for example, aldosterone antagonists, alpha-adrenergic receptor antagonists, antidiabetic compounds, anti-hyperlipidemic drugs, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antioxidants, antithrombotic and vasodilator drugs, beta-adrenergic blockers, calcium channel blockers, diuretics, endothelin antagonists, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and mixtures of two or more thereof. In this embodiment of the invention, the methods can involve administering the nitrosated and/or nitrosylated pyruvate compounds, administering the pyruvate compounds, that are optionally nitrosated and/or nitrosylated, and NO donors, administering the pyruvate compounds, that are optionally nitrosated and/or nitrosylated, and therapeutic agents or administering the pyruvate compounds, that are optionally nitrosated and/or nitrosylated, NO donors, and therapeutic agents. The nitrosated and/or nitrosylated pyruvate compounds, nitric oxide donors, and/or therapeutic agents can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers.

In yet another embodiment the invention provides kits comprising at least one pyruvate compound, that is optionally nitrosated and/or nitrosylated, and, optionally, at least one compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium (NO^+) or nitroxyl (NO-), or as the neutral species, nitric oxide (NO•), and/or stimulates endogenous production of nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase. The kit can further comprise at least one therapeutic agent, such as, for example,

aldosterone antagonists, alpha-adrenergic receptor antagonists, antidiabetic compounds, anti-hyperlipidemic drugs, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antioxidants, antithrombotic and vasodilator drugs, beta-adrenergic blockers, calcium channel blockers, diuretics, endothelin antagonists, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and mixtures of two or more thereof. The pyruvate compound, the nitric oxide donor and/or therapeutic agent, can be separate components in the kit or can be in the form of a composition in one or more pharmaceutically acceptable carriers.

These and other aspects of the invention are described in detail herein.

DETAILED DESCRIPTION OF THE INVENTION

As used throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings.

"Pyruvate compound" refers to and includes derivatives of pyruvic acid such as for example oximes, amides, pyruvate analogues, modified pyruvate analogues, pyruvate esters (for example polyol-pyruvate esters, pyruvate thioesters, glycerol-pyruvate esters, dibydroxyacetone pyruvate esters, and the like), pyruvyl-amino acids (for example pyruvyl-glycine, pyruvyl-gluatamic, pyruvyl-alanine, pyruvyl-leucine, pyruvyl-valine, pyruvyl-isoleucine, pyruvyl-phenylalanine, pyruvyl-cysteine, pyruvyl-proline, pyruvyl-sarcosine, and their amides and esters the like); pyruvate di-, tri- or tetra peptides (such as for example glutamine-cystein-pyruvate, glutamine-cysteine-glycine-pyruvate and the like).

"Diseases resulting from oxidative stress" refers to any disease that involves the generation of free radicals or radical compounds, such as, for example, cardiovascular diseases, neurological or neurodegeneration disorders, inflammatory diseases, respiratory diseases, vascular hypertrophy associated with hypertension, aging, parathyroidal reactive hyperplasia, acute or chronic renal disease, neoplastic diseases, muscle fatigue, tumorigenesis, ischemia reperfusion, sepsis, reperfusion injury, liver toxicity, and the like.

"Cardiovascular diseases" refers to any cardiovascular disease, including but not limited to, congestive heart failure, restenosis, hypertension (e.g. pulmonary hypertension, low-renin hypertension, salt-sensitive hypertension, low-renin, salt-sensitive hypertension, thromboembolic

pulmonary hypertension; pregnancy-induced hypertension; renovascular hypertension; hypertension-dependent end-stage renal disease, and the like), myocardial infarctions, cerebral infarctions, atherosclerosis, atherogenesis, thrombosis, aneurysm, ischemic heart disease, cerebral ischemia, myocardial ischemia, diastolic dysfunction, post-angioplasty restenosis, coronary artery diseases, coronary plaque inflammation, acute or chronic renal failure, stable, unstable and variant (Prinzmetal) angina, hypercholesterolemia, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, embolism, stroke, shock, arrhythmia, atrial fibrillation or atrial flutter, transient ischemic attacks, thrombotic occlusion and reclusion cerebrovascular incidents, hypertension, platelet adhesion, platelet aggregation, smooth muscle cell proliferation, vascular complications associated with the use of medical devices, wounds associated with the use of medical devices, vascular grafting, coronary artery bypass surgery, thromboembolic events, and the like.

"Restenosis" is a cardiovascular disease or disorder that refers to the closure of a peripheral or coronary artery following trauma to the artery caused by an injury such as, for example, angioplasty, balloon dilation, atherectomy, laser ablation treatment or stent insertion. Restenosis can also occur following a number of invasive surgical techniques, such as, for example, transplant surgery, vein grafting, coronary artery bypass surgery, endarterectomy, heart transplantation, balloon angioplasty, atherectomy, laser ablation, endovascular stenting, and the like.

"Atherosclerosis" is a form of chronic vascular injury in which some of the normal vascular smooth muscle cells in the artery wall, which ordinarily control vascular tone regulating blood flow, change their nature and develop "cancer-like" behavior. These vascular smooth muscle cells become abnormally proliferative, secreting substances such as growth factors, tissue-degradation enzymes and other proteins, which enable them to invade and spread into the inner vessel lining, blocking blood flow and making that vessel abnormally susceptible to being completely blocked by local blood clotting, resulting in the death of the tissue served by that artery. Atherosclerotic cardiovascular disease, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease and peripheral vessel disease are all common manifestations of atherosclerosis and are therefore encompassed by the terms "atherosclerosis" and "atherosclerotic disease".

"Thromboembolic events" include, but is not limited to, ischemic stroke, transient ischemic stroke, myocardial infarction, angina pectoris, thrombosis (for example, restenosis, arterial thrombosis, coronary thrombosis, heart valve thrombosis, coronary stenosis, stent thrombosis, graft thrombosis, and first and subsequent thrombotic stroke, and the like), thromboembolism (for example, pulmonary thromboembolism, cerebral thromboembolism, and the like), thrombophlebitis, thrombocytopenia, bleeding disorders, thrombotic occlusion and reocclusion, acute vascular events. Patients who are at risk of developing thromboembolic events, may include those with a familial history of, or genetically predisposed to, thromboembolic disorders, who have had ischemic stroke, transient ischemic stroke, myocardial infarction, and those with unstable angina pectoris or chronic stable angina pectoris and patients with altered prostacyclin/thromboxane A_2 homeostasis or higher than normal thromboxane A_2 levels leading to increase risk for thromboembolism, including patients with diabetes and rheumatoid arthritis.

"Neurological or neurodegenerative disorders" refers to and includes Alzheimer's disease, dementia, Parkinson's disease, cognitive dysfunction, post-surgurical conginive dysfunction, periphal neuropathy including but not limited to, spinal cord injury, head injury, surgical trauma and the like.

"Inflammatory diseases" refers to and includes, include, for example, cardiovascular disorder, reperfusion injury to an ischemic organ, autoimmune disease, angiogenisis, arthritis, including but not limited to rheumatoid arthritis, degenerative joint disease (osteoarthritis), spondyloarthropathies, gouty arthritis, systemic lupus erythematosus and juvenile arthritis; asthma, bronchitis, premature labor, tendinitis, bursitis; autoimmune diseases, immunological disorders; skin-related conditions, such as, for example, psoriasis, eczema, surface wounds, burns and dermatitis, skin ulcers, skin wounds; post-operative inflammation including from ophthalmic surgery, such as, for example, cataract surgery and refractive surgery, and the like; neoplasia, such as, for example, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma), such as, for example, basal cell carcinoma, adenocarcinoma, gastrointestinal cancer, lip cancer, mouth cancer, esophageal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamus cell and basal cell cancers, prostate cancer, renal

cell carcinoma, and other known cancers that effect epithelial cells throughout the body, benign and cancerous tumors, growths, polyps, adenomatous polyps, including, but not limited to, familial adenomatous polyposis, fibrosis resulting from radiation therapy, and the like; inflammatory processes in diseases, such as, for example, vascular diseases, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like; pulmonary inflammation, such as, for example, those associated with viral infections and cystic fibrosis, and the like; central nervous system disorders, such as, for example, cortical dementia including Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, memory loss and central nervous system damage resulting from stroke, ischemia and trauma, and the like; allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, inflammations and/or microbial infections including, for example, inflammations and/or infections of the eyes, ears, nose, throat, and/or skin; bacterial-induced inflammation, such as, for example, *Chlamydia*-induced inflammation; viral induced inflammation, urinary and/or urological disorders, such as, for example, incontinence and the like; cytokine-mediated inflammatory diseases, such as, for example, inflammatory conditions mediated by an early tumor necrosis factor, interleukin 1β or late high mobility group such as for example, local or systemic inflammation, inflammatory bowel disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, asthma, sepsis, septic shock; endothelial dysfunctions, such as, for example, diseases accompanying these dysfunctions, endothelial damage from hypercholesterolemia, endothelial damage from hypoxia, endothelial damage from mechanical and chemical noxae, especially during and after drug, and mechanical reopening of stenosed vessels, for example, following percutaneous transluminal angiography (PTA) and percuntaneous transluminal coronary angiography (PTCA), endothelial damage in postinfarction phase, endothelium-mediated reocculusion following bypass surgery, blood supply distrubances in peripheral arteries, and the like; sexual dysfunctions in men and women; tissue deterioration, such as, for example, for organ transplant rejection, and the like; disorders treated by the inhibition and/or prevention of activation, adhesion and infiltration of neutrophils at the site of

inflammation; and disorders treated by the inhibition and/or prevention of platelet aggregation.

"Respiratory diseases" refers to an includes any respiratory disease or disorder, such as, for example, acute pulmonary vasoconstriction, pneumonia, traumatic injury, aspiration or inhalation injury, fat embolism in the lung, acidosis, inflammation of the lung, adult respiratory distress syndrome, acute pulmonary edema, acute mountain sickness, asthma, cystic fibrosis, post cardiac surgery, acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reactions, sepsis, status asthmaticus, hypoxia, chronic pulmonary hypertension, bronchopulmonary dysplasia, chronic pulmonary thromboembolism, idiopathic pulmonary hypertension, primary pulmonary hypertension or chronic hypoxia.

"Antioxidant" refers to and includes any compound that can react and quench a free radical.

"Angiotensin converting enzyme (ACE) inhibitor" refers to compounds that inhibit an enzyme which catalyzes the conversion of angiotensin I to angiotensin II. ACE inhibitors include, but are not limited to, amino acids and derivatives thereof, peptides, including di- and tri-peptides, and antibodies to ACE which intervene in the renin-angiotensin system by inhibiting the activity of ACE thereby reducing or eliminating the formation of the pressor substance angiotensin II.

"Angiotensin II antagonists" refers to compounds which interfere with the function, synthesis or catabolism of angiotensin II. Angiotensin II antagonists include peptide compounds and non-peptide compounds, including, but not limited to, angiotensin II antagonists, angiotensin II receptor antagonists, agents that activate the catabolism of angiotensin II, and agents that prevent the synthesis of angiotensin I from angiotensin II. The renin-angiotensin system is involved in the regulation of hemodynamics and water and electrolyte balance. Factors that lower blood volume, renal perfusion pressure, or the concentration of sodium in plasma tend to activate the system, while factors that increase these parameters tend to suppress its function.

"Anti-hyperlipidemic drugs" refers to any compound or agent that has the effect of beneficially modifying serum cholesterol levels such as, for example, lowering serum low density lipoprotein (LDL) cholesterol levels, or inhibiting oxidation of LDL cholesterol, whereas high density lipoprotein (HDL) serum cholesterol levels may be lowered, remain the same, or be

increased. Preferably, the anti-hyperlipidemic drug brings the serum levels of LDL cholesterol and HDL cholesterol (and, more preferably, triglyceride levels) to normal or nearly normal levels.

"Neutral endopeptidase inhibitors" refers to and includes compounds that are antagonists of the renin angiotensin aldosterone system including compounds that are dual inhibitors of neutral endopeptidases and angiotensin converting (ACE) enzymes.

"Renin inhibitors" refers to compounds which interfere with the activity of renin.

"Platelet reducing agents" refers to compounds that prevent the formation of a blood thrombus via any number of potential mechanisms. Platelet reducing agents include, but are not limited to, fibrinolytic agents, anti-coagulant agents and any inhibitors of platelet function. Inhibitors of platelet function include agents that impair the ability of mature platelets to perform their normal physiological roles (i.e., their normal function, such as, for example, adhesion to cellular and non-cellular entities, aggregation, release of factors such as growth factors) and the like.

"Proton pump inhibitor" refers to any compound that reversibly or irreversibly blocks gastric acid secretion by inhibiting the H^+/K^+-ATP ase enzyme system at the secretory surface of the gastric parietal cell.

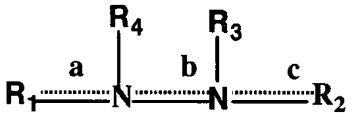
"NSAID" refers to a nonsteroidal anti-inflammatory compound or a nonsteroidal anti-inflammatory drug. NSAIDs inhibit cyclooxygenase, the enzyme responsible for the biosyntheses of the prostaglandins and certain autocoid inhibitors, including inhibitors of the various isozymes of cyclooxygenase (including but not limited to cyclooxygenase-1 and -2), and as inhibitors of both cyclooxygenase and lipoxygenase.

"Therapeutic agent" includes any therapeutic agent that can be used to treat or prevent the diseases described herein. "Therapeutic agents" include, for example, aldosterone antagonists, alpha-adrenergic receptor antagonists, antidiabetic compounds, anti-hyperlipidemic drugs, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antioxidants, antithrombotic and vasodilator drugs, beta-adrenergic blockers, calcium channel blockers, diuretics, endothelin antagonists, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), potassium channel blockers, platelet reducing agents, proton pump inhibitor, renin inhibitors, selective cyclooxygenase-2 (COX-2)

inhibitors, and the like. Therapeutic agent includes the pro-drugs and pharmaceutical derivatives thereof including, but not limited to, the corresponding nitrosated and/or nitrosylated derivatives. Although nitric oxide donors have therapeutic activity, the term "therapeutic agent" does not include the nitric oxide donors described herein, since nitric oxide donors are separately defined.

"Cyclooxygenase-2 (COX-2) selective inhibitor" refers to a compound that selectively inhibits the cyclooxygenase-2 enzyme over the cyclooxygenase-1 enzyme. In one embodiment, the compound has a cyclooxygenase-2 IC_{50} of less than about 2 μM and a cyclooxygenase-1 IC_{50} of greater than about 5 μM, in the human whole blood COX-2 assay (as described in Brideau et al., *Inflamm Res.*, 45: 68-74 (1996)) and also has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 10, and preferably of at least 40. In another embodiment, the compound has a cyclooxygenase-1 IC_{50} of greater than about 1 μM, and preferably of greater than 20 μM. The compound can also inhibit the enzyme, lipoxygenase. Such selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

"Hydralazine compound" refers to a compound having the formula:



wherein a, b and c are independently a single or double bond; $R_1$and R_2 are each independently a hydrogen, an alkyl, an ester or a heterocyclic ring, wherein alkyl, ester and heterocyclic rind are as defined herein; R_3 and R_4 are each independently a lone pair of electrons or a hydrogen, with the proviso that at least one of R_1, R_2, R_3 and R_4 is not a hydrogen. Exemplary hydralazine compounds include budralazine, cadralazine, dihydralazine, endralazine, hydralazine, pildralazine, todralazine, and the like.

"Patient" refers to animals, preferably mammals, most preferably humans, and includes males and females, and children and adults.

"Therapeutically effective amount" refers to the amount of the compound and/or composition that is effective to achieve its intended purpose.

"Transdermal" refers to the delivery of a compound by passage through the skin and into the blood stream.

"Transmucosal" refers to delivery of a compound by passage of the compound through the mucosal tissue and into the blood stream.

"Penetration enhancement" or "permeation enhancement" refers to an increase in the permeability of the skin or mucosal tissue to a selected pharmacologically active compound such that the rate at which the compound permeates through the skin or mucosal tissue is increased.

"Carriers" or "vehicles" refers to carrier materials suitable for compound administration and include any such material known in the art such as, for example, any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is non-toxic and which does not interact with any components of the composition in a deleterious manner.

"Sustained release" refers to the release of a therapeutically active compound and/or composition such that the blood levels of the therapeutically active compound are maintained within a desirable therapeutic range over an extended period of time. The sustained release formulation can be prepared using any conventional method known to one skilled in the art to obtain the desired release characteristics.

"Nitric oxide adduct" or "NO adduct" refers to compounds and functional groups which, under physiological conditions, can donate, release and/or directly or indirectly transfer any of the three redox forms of nitrogen monoxide (NO^+, NO^-, NO•), such that the biological activity of the nitrogen monoxide species is expressed at the intended site of action.

"Nitric oxide releasing" or "nitric oxide donating" refers to methods of donating, releasing and/or directly or indirectly transferring any of the three redox forms of nitrogen monoxide (NO^+, NO^-, NO•), such that the biological activity of the nitrogen monoxide species is expressed at the intended site of action.

"Nitric oxide donor" or "NO donor" refers to compounds that donate, release and/or directly or indirectly transfer a nitrogen monoxide species, and/or stimulate the endogenous production of nitric oxide or endothelium-derived relaxing factor (EDRF) *in vivo* and/or elevate endogenous levels of nitric oxide or EDRF *in vivo*. "NO donor" also includes compounds that are substrates for nitric oxide synthase.

"Alkyl" refers to a lower alkyl group, a substituted lower alkyl group, a haloalkyl group, a hydroxyalkyl group, an alkenyl group, a substituted alkenyl group, an alkynyl group, a bridged cycloalkyl group, a cycloalkyl group or a heterocyclic ring, as defined herein. An alkyl group

may also comprise one or more radical species, such as, for example a cycloalkylalkyl group or a heterocyclicalkyl group.

"Lower alkyl" refers to branched or straight chain acyclic alkyl group comprising one to about ten carbon atoms (preferably one to about eight carbon atoms, more preferably one to about six carbon atoms). Exemplary lower alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, neopentyl, iso-amyl, hexyl, octyl, and the like.

"Substituted lower alkyl" refers to a lower alkyl group, as defined herein, wherein one or more of the hydrogen atoms have been replaced with one or more R^{100} groups, wherein each R^{100} is independently a hydroxy, an ester, an amidyl, an oxo, a carboxyl, a carboxamido, a halo, a cyano, a nitrate or an amino group, as defined herein.

"Haloalkyl" refers to a lower alkyl group, an alkenyl group, an alkynyl group, a bridged cycloalkyl group, a cycloalkyl group or a heterocyclic ring, as defined herein, to which is appended one or more halogens, as defined herein. Exemplary haloalkyl groups include trifluoromethyl, chloromethyl, 2-bromobutyl, 1-bromo-2-chloro-pentyl, and the like.

"Alkenyl" refers to a branched or straight chain C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) that can comprise one or more carbon-carbon double bonds. Exemplary alkenyl groups include propylenyl, buten-1-yl, isobutenyl, penten-1-yl, 2,2-methylbuten-1-yl, 3-methylbuten-1-yl, hexan-1-yl, hepten-1-yl, octen-1-yl, and the like.

"Lower alkenyl" refers to a branched or straight chain C_2-C_4 hydrocarbon that can comprise one or two carbon-carbon double bonds.

"Substituted alkenyl" refers to a branched or straight chain C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) which can comprise one or more carbon-carbon double bonds, wherein one or more of the hydrogen atoms have been replaced with one or more R^{100} groups, wherein each R^{100} is independently a hydroxy, an oxo, a carboxyl, a carboxamido, a halo, a cyano or an amino group, as defined herein.

"Alkynyl" refers to an unsaturated acyclic C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) that can comprise one or more carbon-carbon triple bonds. Exemplary alkynyl groups include ethynyl, propynyl, butyn-1-yl, butyn-2-yl,

pentyl-1-yl, pentyl-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyl-2-yl, hexyl-3-yl, 3,3-dimethyl-butyn-1-yl, and the like.

"Bridged cycloalkyl" refers to two or more cycloalkyl groups, heterocyclic groups, or a combination thereof fused via adjacent or non-adjacent atoms. Bridged cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, carboxyl, alkylcarboxylic acid, aryl, amidyl, ester, alkylcarboxylic ester, carboxamido, alkylcarboxamido, oxo and nitro. Exemplary bridged cycloalkyl groups include adamantyl, decahydronapthyl, quinuclidyl, 2,6-dioxabicyclo(3.3.0)octane, 7-oxabicyclo(2.2.1)heptyl, 8-azabicyclo(3,2,1)oct-2-enyl and the like.

"Cycloalkyl" refers to a saturated or unsaturated cyclic hydrocarbon comprising from about 3 to about 10 carbon atoms. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, aryl, amidyl, ester, hydroxy, halo, carboxyl, alkylcarboxylic acid, alkylcarboxylic ester, carboxamido, alkylcarboxamido, oxo, alkylsulfinyl, and nitro. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like.

"Heterocyclic ring or group" refers to a saturated or unsaturated cyclic hydrocarbon group having about 2 to about 10 carbon atoms (preferably about 4 to about 6 carbon atoms) where 1 to about 4 carbon atoms are replaced by one or more nitrogen, oxygen and/or sulfur atoms. Sulfur maybe in the thio, sulfinyl or sulfonyl oxidation state. The heterocyclic ring or group can be fused to an aromatic hydrocarbon group. Heterocyclic groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylthio, aryloxy, arylthio, arylalkyl, hydroxy, oxo, thial, halo, carboxyl, carboxylic ester, alkylcarboxylic acid, alkylcarboxylic ester, aryl, arylcarboxylic acid, arylcarboxylic ester, amidyl, ester, alkylcarbonyl, arylcarbonyl, alkylsulfinyl, carboxamido, alkylcarboxamido, arylcarboxamido, sulfonic acid, sulfonic ester, sulfonamido and nitro. Exemplary heterocyclic groups include pyrrolyl, furyl, thienyl, 3-pyrrolinyl,4,5,6-trihydro-2H-pyranyl, pyridinyl, 1,4-dihydropyridinyl, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrhydrofuranyl, tetrazolyl, pyrrolinyl, pyrrolindinyl, oxazolindinyl 1,3-dioxolanyl, imidazolinyl, imidazolindinyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-

oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazolyl, benzothiazolinyl, quinolinyl, 2,6-dioxabicyclo(3.3.0)octane, and the like.

"Heterocyclic compounds" refer to mono- and polycyclic compounds comprising at least one aryl or heterocyclic ring.

"Aryl" refers to a monocyclic, bicyclic, carbocyclic or heterocyclic ring system comprising one or two aromatic rings. Exemplary aryl groups include phenyl, pyridyl, napthyl, quinoyl, tetrahydronaphthyl, furanyl, indanyl, indenyl, indoyl, and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, alkylthio, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, halo, cyano, alkylsulfinyl, hydroxy, carboxyl, carboxylic ester, alkylcarboxylic acid, alkylcarboxylic ester, aryl, arylcarboxylic acid, arylcarboxylic ester, alkylcarbonyl, arylcarbonyl, amidyl, ester, carboxamido, alkylcarboxamido, carbomyl, sulfonic acid, sulfonic ester, sulfonamido and nitro. Exemplary substituted aryl groups include tetrafluorophenyl, pentafluorophenyl, sulfonamide, alkylsulfonyl, arylsulfonyl, and the like.

"Cycloalkenyl" refers to an unsaturated cyclic C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) which can comprise one or more carbon-carbon triple bonds.

"Alkylaryl" refers to an alkyl group, as defined herein, to which is appended an aryl group, as defined herein. Exemplary alkylaryl groups include benzyl, phenylethyl, hydroxybenzyl, fluorobenzyl, fluorophenylethyl, and the like.

"Arylalkyl" refers to an aryl radical, as defined herein, attached to an alkyl radical, as defined herein. Exemplary arylalkyl groups include benzyl, phenylethyl, 4-hydroxybenzyl, 3-fluorobenzyl, 2-fluorophenylethyl, and the like.

"Arylalkenyl" refers to an aryl radical, as defined herein, attached to an alkenyl radical, as defined herein. Exemplary arylalkenyl groups include styryl, propenylphenyl, and the like.

"Cycloalkylalkyl" refers to a cycloalkyl radical, as defined herein, attached to an alkyl radical, as defined herein.

"Cycloalkylalkoxy" refers to a cycloalkyl radical, as defined herein, attached to an alkoxy radical, as defined herein.

"Cycloalkylalkylthio" refers to a cycloalkyl radical, as defined herein, attached to an alkylthio radical, as defined herein.

"Heterocyclicalkyl" refers to a heterocyclic ring radical, as defined herein, attached to an alkyl radical, as defined herein.

"Arylheterocyclic ring" refers to a bi- or tricyclic ring comprised of an aryl ring, as defined herein, appended via two adjacent carbon atoms of the aryl ring to a heterocyclic ring, as defined herein. Exemplary arylheterocyclic rings include dihydroindole, 1,2,3,4-tetra-hydroquinoline, and the like.

"Alkylheterocyclic ring" refers to a heterocyclic ring radical, as defined herein, attached to an alkyl radical, as defined herein. Exemplary alkylheterocyclic rings include 2-pyridylmethyl, 1-methylpiperidin-2-one-3-methyl, and the like.

"Alkoxy" refers to $R_{50}O$-, wherein R_{50} is an alkyl group, as defined herein (preferably a lower alkyl group or a haloalkyl group, as defined herein). Exemplary alkoxy groups include methoxy, ethoxy, t-butoxy, cyclopentyloxy, trifluoromethoxy, and the like.

"Aryloxy" refers to $R_{55}O$-, wherein R_{55} is an aryl group, as defined herein. Exemplary arylkoxy groups include napthyloxy, quinolyloxy, isoquinolizinyloxy, and the like.

"Alkylthio" refers to $R_{50}S$-, wherein R_{50} is an alkyl group, as defined herein.

"Lower alkylthio" refers to a lower alkyl group, as defined herein, appended to a thio group, as defined herein.

"Arylalkoxy" or "alkoxyaryl" refers to an alkoxy group, as defined herein, to which is appended an aryl group, as defined herein. Exemplary arylalkoxy groups include benzyloxy, phenylethoxy, chlorophenylethoxy, and the like.

"Alkoxyalkyl" refers to an alkoxy group, as defined herein, appended to an alkyl group, as defined herein. Exemplary alkoxyalkyl groups include methoxymethyl, methoxyethyl, isopropoxymethyl, and the like.

"Alkoxyhaloalkyl" refers to an alkoxy group, as defined herein, appended to a haloalkyl group, as defined herein. Exemplary alkoxyhaloalkyl groups include 4- methoxy-2-chlorobutyl and the like.

"Cycloalkoxy" refers to $R_{54}O$-, wherein R_{54} is a cycloalkyl group or a bridged cycloalkyl group, as defined herein. Exemplary cycloalkoxy groups include cyclopropyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

"Cycloalkylthio" refers to $R_{54}S$-, wherein R_{54} is a cycloalkyl group or a bridged cycloalkyl group, as defined herein. Exemplary cycloalkylthio groups include cyclopropylthio, cyclopentylthio, cyclohexylthio, and the like.

"Haloalkoxy" refers to an alkoxy group, as defined herein, in which one or more of the hydrogen atoms on the alkoxy group are substituted with halogens, as defined herein. Exemplary haloalkoxy groups include 1,1,1-trichloroethoxy, 2-bromobutoxy, and the like.

"Hydroxy" refers to -OH.

"Oxo " refers to =O.

"Oxy " refers to $-O^- R_{77}^+$ wherein R_{77} is an organic or inorganic cation.

"Oxime" refers to $=N-OR_{81}$ wherein $R_{81}$is a hydrogen, an alkyl group, an aryl group, an alkylsulfonyl group, an arylsulfonyl group, a carboxylic ester, an alkylcarbonyl group, an arylcarbonyl group, a carboxamido group, an alkoxyalkyl group or an alkoxyaryl group.

"Hydrazone refers to $=N-N(R_{81})(R'_{81})$ wherein R'_{81} is independently selected from R_{81}, and R_{81} is as defined herein.

"Hydrazino" refers to $H_2N-N(H)$-.

"Organic cation" refers to a positively charged organic ion. Exemplary organic cations include alkyl substituted ammonium cations, and the like.

"Inorganic cation" refers to a positively charged metal ion. Exemplary inorganic cations include Group I metal cations such as for example, sodium, potassium, magnesium, calcium, and the like.

"Hydroxyalkyl" refers to a hydroxy group, as defined herein, appended to an alkyl group, as defined herein.

"Nitrate" refers to $-O-NO_2$.

"Nitrite" refers to -O-NO.

"Thionitrate" refers to $-S-NO_2$.

"Thionitrite" and "nitrosothiol" refer to -S-NO.

"Nitro" refers to the group $-NO_2$ and "nitrosated" refers to compounds that have been

substituted therewith.

"Nitroso" refers to the group -NO and "nitrosylated" refers to compounds that have been substituted therewith.

"Nitrile" and "cyano" refer to -CN.

"Halogen" or "halo" refers to iodine (I), bromine (Br), chlorine (Cl), and/or fluorine (F).

"Amino " refers to $-NH_2$, an alkylamino group, a dialkylamino group, an arylamino group, a diarylamino group, an alkylarylamino group or a heterocyclic ring, as defined herein.

"Alkylamino" refers to $R_{50}NH$-, wherein R_{50} is an alkyl group, as defined herein. Exemplary alkylamino groups include methylamino, ethylamino, butylamino, cyclohexylamino, and the like.

"Arylamino" refers to $R_{55}NH$-, wherein R_{55} is an aryl group, as defined herein.

"Dialkylamino" refers to $R_{52}R_{53}N$-, wherein R_{52} and R_{53} are each independently an alkyl group, as defined herein. Exemplary dialkylamino groups include dimethylamino, diethylamino, methyl propargylamino, and the like.

"Diarylamino" refers to $R_{55}R_{60}N$-, wherein R_{55} and R_{60} are each independently an aryl group, as defined herein.

"Alkylarylamino or arylalkylamino" refers to $R_{52}R_{55}N$-, wherein R_{52} is an alkyl group, as defined herein, and R_{55} is an aryl group, as defined herein.

"Alkylarylalkylamino " refers to $R_{52}R_{79}N$-, wherein R_{52} is an alkyl group, as defined herein, and R_{79} is an arylalkyl group, as defined herein.

"Alkylcycloalkylamino " refers to $R_{52}R_{80}N$-, wherein R_{52} is an alkyl group, as defined herein, and R_{80} is an cycloalkyl group, as defined herein.

"Aminoalkyl " refers to an amino group, an alkylamino group, a dialkylamino group, an arylamino group, a diarylamino group, an alkylarylamino group or a heterocyclic ring, as defined herein, to which is appended an alkyl group, as defined herein. Exemplary aminoalkyl groups include dimethylaminopropyl, diphenylaminocyclopentyl, methylaminomethyl, and the like.

"Aminoaryl " refers to an aryl group to which is appended an alkylamino group, a arylamino group or an arylalkylamino group. Exemplary aminoaryl groups include anilino, N-methylanilino, N-benzylanilino, and the like.

"Thio" refers to –S-.

"Sulfinyl" refers to -S(O)-.

"Methanthial" refers to -C(S)-.

"Thial" refers to =S.

"Sulfonyl" refers to $-S(O)_2^-$.

"Sulfonic acid" refers to $-S(O)_2OR_{76}$, wherein R_{76} is a hydrogen, an organic cation or an inorganic cation, as defined herein.

"Alkylsulfonic acid" refers to a sulfonic acid group, as defined herein, appended to an alkyl group, as defined herein.

"Arylsulfonic acid" refers to a sulfonic acid group, as defined herein, appended to an aryl group, as defined herein

"Sulfonic ester" refers to $-S(O)_2OR_{58}$, wherein R_{58} is an alkyl group, an aryl group, or an aryl heterocyclic ring, as defined herein.

"Sulfonamido" refers to $-S(O)_2-N(R_{51})(R_{57})$, wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} when taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Alkylsulfonamido" refers to a sulfonamido group, as defined herein, appended to an alkyl group, as defined herein.

"Arylsulfonamido" refers to a sulfonamido group, as defined herein, appended to an aryl group, as defined herein.

"Alkylthio" refers to $R_{50}S-$, wherein R_{50} is an alkyl group, as defined herein (preferably a lower alkyl group, as defined herein).

"Arylthio" refers to $R_{55}S-$, wherein R_{55} is an aryl group, as defined herein.

"Arylalkylthio" refers to an aryl group, as defined herein, appended to an alkylthio group, as defined herein.

"Alkylsulfinyl" refers to $R_{50}-S(O)-$, wherein R_{50} is an alkyl group, as defined herein.

"Alkylsulfonyl" refers to $R_{50}-S(O)_2-$, wherein R_{50} is an alkyl group, as defined herein.

"Alkylsulfonyloxy" refers to $R_{50}-S(O)_2-O-$, wherein R_{50} is an alkyl group, as defined herein.

"Arylsulfinyl" refers to $R_{55}-S(O)-$, wherein R_{55} is an aryl group, as defined herein.

"Arylsulfonyl" refers to R_{55}-$S(O)_2$-, wherein R_{55} is an aryl group, as defined herein.

"Arylsulfonyloxy" refers to R_{55}-$S(O)_2$-O-, wherein R_{55} is an aryl group, as defined herein.

"Amidyl" refers to $R_{51}C(O)N(R_{57})$- wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein.

"Ester" refers to $R_{51}C(O)R_{76}$- wherein R_{51} is a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein and R_{76} is oxygen or sulfur.

"Carbamoyl" refers to -O-$C(O)N(R_{51})(R_{57})$, wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Carboxyl" refers to $-C(O)OR_{76}$, wherein R_{76} is a hydrogen, an organic cation or an inorganic cation, as defined herein.

"Carbonyl" refers to –C(O)-.

"Alkylcarbonyl" refers to R_{52}-C(O)-, wherein R_{52} is an alkyl group, as defined herein.

"Arylcarbonyl" refers to R_{55}-C(O)-, wherein R_{55} is an aryl group, as defined herein.

"Arylalkylcarbonyl" refers to R_{55}-R_{52}-C(O)-, wherein R_{55} is an aryl group, as defined herein, and R_{52} is an alkyl group, as defined herein.

"Alkylarylcarbonyl" refers to R_{52}-R_{55}-C(O)-, wherein R_{55} is an aryl group, as defined herein, and R_{52} is an alkyl group, as defined herein.

"Heterocyclicalkylcarbonyl" refer to $R_{78}C(O)$- wherein R_{78} is a heterocyclicalkyl group, as defined herein.

"Carboxylic ester" refers to -$C(O)OR_{58}$, wherein R_{58} is an alkyl group, an aryl group or an aryl heterocyclic ring, as defined herein.

"Alkylcarboxylic acid" and "alkylcarboxyl" refer to an alkyl group, as defined herein, appended to a carboxyl group, as defined herein.

"Alkylcarboxylic ester" refers to an alkyl group, as defined herein, appended to a carboxylic ester group, as defined herein.

"Alkyl ester" refers to an alkyl group, as defined herein, appended to an ester group, as defined herein.

"Arylcarboxylic acid" refers to an aryl group, as defined herein, appended to a carboxyl

group, as defined herein.

"Arylcarboxylic ester" and "arylcarboxyl" refer to an aryl group, as defined herein, appended to a carboxylic ester group, as defined herein.

"Aryl ester" refers to an aryl group, as defined herein, appended to an ester group, as defined herein.

"Carboxamido" refers to -C(O)N(R_{51})(R_{57}), wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} when taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Alkylcarboxamido" refers to an alkyl group, as defined herein, appended to a carboxamido group, as defined herein.

"Arylcarboxamido" refers to an aryl group, as defined herein, appended to a carboxamido group, as defined herein.

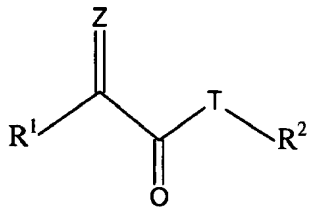
"Urea" refers to -N(R_{59})-C(O)N(R_{51})(R_{57}) wherein R_{51}, R_{57}, and R_{59} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Phosphoryl" refers to -P(R_{70})(R_{71})(R_{72}), wherein R_{70} is a lone pair of electrons, thial or oxo, and R_{71} and R_{72} are each independently a covalent bond, a hydrogen, a lower alkyl, an alkoxy, an alkylamino, a hydroxy, an oxy or an aryl, as defined herein.

"Silyl" refers to -Si(R_{73})(R_{74})(R_{75}), wherein R_{73}, R_{74} and R_{75} are each independently a covalent bond, a lower alkyl, an alkoxy, an aryl or an arylalkoxy, as defined herein.

The invention is directed to the treatment of diseases resulting from oxidative stress, diabetes, reperfusion injury following ischemia, and to the preservation of tissues, organs, organ parts and/or limbs comprising administering to the patient a therapeutically effective amount of at least one pyruvate compound, that is optionally substituted with at least one NO_2 and/or NO group (i.e., nitrosated and/or nitrosylated). Preferably, the pyruvate compounds that are linked to one or more nitric oxide groups are administered in the form of a pharmaceutical composition that further comprises a pharmaceutically acceptable carrier or diluent. The novel compounds and novel compositions of the invention are described in more detail herein.

In one embodiment, the invention describes nitrosated and/or nitrosylated pyruvate compounds and pharmaceutically acceptable salts thereof, of Formula (I);

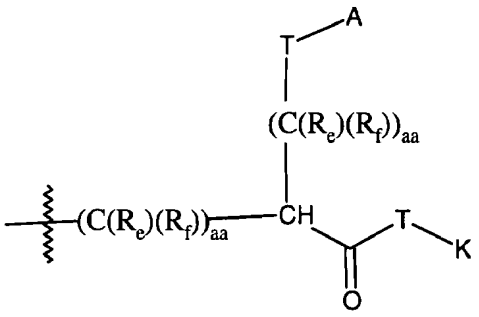


(I)

wherein:

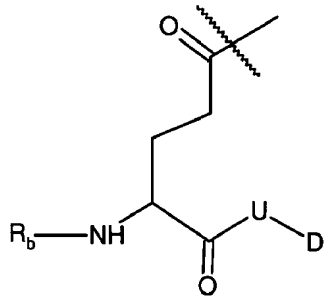
R^1 is K' or $-(C(R_e)(R_f))_{aa}$-T-A;

R^2 is K or

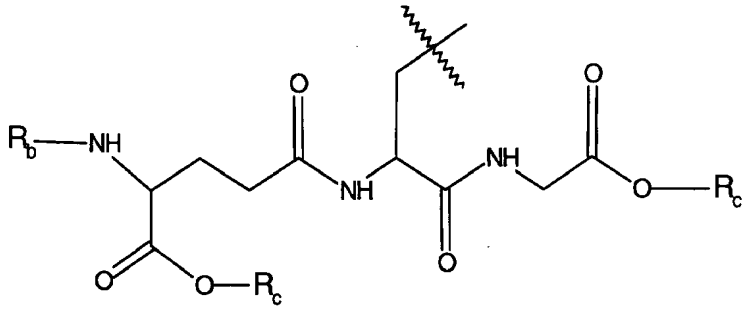


;

A is a hydrogen, K, K',



or



;

R_b is a hydrogen, a lower alkyl group or $-COCH_3$;

R_c is a hydrogen or a lower alkyl group;

D is a hydrogen, V or K;

U is oxygen, sulfur or $-N(R_a)R_i$;

Z is an oxo, an oxime, a hydrozone, =N-O-A, -N-(OA)-R_{82}, =N-N-(A)(R_{82}) or =N-(R_{82});

R_{82} is a hydrogen, K, an alkyl group, an aryl group, an alkylsulfonyl group, an

arylsulfonyl group, a carboxylic ester, an alkylcarbonyl group, an arylcarbonyl group, a carboxamido group, an alkoxyalkyl group or an alkoxyaryl group;

K is $-W_a-E_b-(C(R_e)(R_f))_p-E_c-(C(R_e)(R_f))_x-W_d-(C(R_e)(R_f))_y-W_i-E_j-W_g-(C(R_e)(R_f))_z-U-V$;

K' is $-W_a-E_b-(C(R_e)(R_f))_p-E_c-(C(R_e)(R_f))_x-W_d-(C(R_e)(R_f))_y-W_i-E_j-W_g-(C(R_e)(R_f))_z-R_e$;

V is –NO or $–NO_2$;

a, b, c, d, g, i and j are each independently an integer from 0 to 3;

aa is an integer from 0 to 5;

p, x, y and z are each independently an integer from 0 to 10;

W at each occurrence is independently -C(O)-, -C(S)-, -T-, $-(C(R_e)(R_f))_h-$, an alkyl group, an aryl group, a heterocyclic ring, a heterocyclic compound, an arylheterocyclic ring, or $-(CH_2CH_2O)_q-$;

E at each occurrence is independently -T-, an alkyl group, an aryl group, $-(C(R_e)(R_f))_h-$, a heterocyclic ring, a heterocyclic compound, an arylheterocyclic ring, or $-(CH_2CH_2O)_q-$;

h is an integer form 1 to 10;

q is an integer from 1 to 5;

R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, an alkylcycloalkyl, an alkylheterocyclic ring, a cycloalkylalkyl, a cycloalkylthio, a cycloalkenyl, an heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, arylsulphonyloxy, a sulfonic ester, an alkyl ester, an aryl ester, a urea, a phosphoryl, a nitro, W_h, $-(CH_2)_o-T-V$, or $-(C(R_g)(R_h))_k-T-V$, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group, an aryl group, an oxime, a hydrazone or a bridged cycloalkyl group;

R_g and R_h at each occurrence are independently R_e;

k is an integer from 1 to 3;

T at each occurrence is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o-$ or $-N(R_a)R_i$;

o is an integer from 0 to 2;

R_a is a lone pair of electrons, a hydrogen or an alkyl group;

R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyl, arylsulphonyloxy, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, $-CH_2-C(T-V)(R_e)(R_f)$, a bond to an adjacent atom creating a double bond to that atom, $-(N_2O_2-)^-\bullet M^+$, wherein M^+ is an organic or inorganic cation; and

with the proviso that the nitrosated and/or nitrosylated compounds of Formula I must contain at least one nitrite, nitrate, thionitrite or thionitrate group.

In cases where multiple designations of variables which reside in sequence are chosen as a "covalent bond" or the integer chosen is 0, the intent is to denote a single covalent bond connecting one radical to another. For example, E_0 would denote a covalent bond, while E_2 denotes (E-E) and $(C(R_4)(R_4))_2$ denotes $-C(R_4)(R_4)-C(R_4)(R_4)-$.

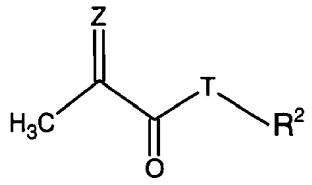
Compounds of the invention that have one or more asymmetric carbon atoms may exist as the optically pure enantiomers, pure diastereomers, mixtures of enantiomers, mixtures of diastereomers, racemic mixtures of enantiomers, diastereomeric racemates or mixtures of diastereomeric racemates. It is to be understood that the invention anticipates and includes within its scope all such isomers and mixtures thereof.

Compounds of the invention that have one or more double bounds may exists as a single tautomers or a mixture of tautomers. It is to be understood that the invention anticipates and includes within its scope all such tautomers and mixtures thereof.

In a preferred embodiment the compounds of Formula (I) do not include the compounds of ACS registry numbers 143277-70-7 and 143253-72-9. These compounds are disclosed in U.S. Patent No. 5,120,737.

In another preferred embodiment the nitrosated and/or nitrosylated pyruvate compounds

and pharmaceutically acceptable salts thereof, of Formula (I) are the compounds of Formula (II):



(II)

wherein Z, T and R^2 are as defined herein.

In yet another preferred embodiment the compounds of Formulas (I) are:

(4-(nitrooxy)piperidyl)methyl-2-oxopropanoate;

2-(4-(nitrooxy)piperidyl)ethyl-2-oxopropanoate;

3-(4-(nitrooxy)piperidyl)propyl-2-oxopropanoate;

1-(4-(nitrooxy)piperidyl)propane-1,2-dione;

(2R)-2,3-bis(nitrooxy)propyl-2-oxopropanoate;

(4-(2-(nitrooxy)ethyl)phenyl)methyl-2-oxopropanoate;

(4-((nitrooxy)methyl)piperzinyl)methyl-2-oxopropanoate;

2-(4-((nitrooxy)methyl)piperzinyl)ethyl-2-oxopropanoate;

3-(4-((nitrooxy)methyl)piperzinyl)propyl-2-oxopropanoate;

(4-(2-(nitrooxy)ethyl)piperzinyl)methyl-2-oxopropanoate;

2-(4-(2-(nitrooxy)ethyl)piperzinyl)ethyl-2-oxopropanoate;

3-(4-(2-(nitrooxy)ethyl)piperzinyl)propyl-2-oxopropanoate;

(4-(3-(nitrooxy)propyl)piperzinyl)methyl-2-oxopropanoate;

2-(4-(3-(nitrooxy)propyl)piperzinyl)ethyl-2-oxopropanoate;

3-(4-(3-(nitrooxy)propyl)piperzinyl)propyl-2-oxopropanoate;

1-(2-((nitrooxy)methyl)piperidyl)propane-1,2-dione;

1-(3-((nitrooxy)methyl)piperidyl)propane-1,2-dione;

1-(4-((nitrooxy)methyl)piperidyl)propane-1,2-dione;

methyl (2*R*)-2-amino-3-((3-((2-(2-(nitrooxy)ethoxy)ethyl)amino)-2,3-dioxopropyl)thio) propanoate;

4-(N-((1R)-1-(methoxycarbonyl)-2-(2-(N-(2-(2-(nitrooxy)ethoxy)ethyl)carbamoyl)-2-oxoethylthio)ethyl)carbamoyl)(2S)-2-aminobutanoic acid;

2-(4-(2-(nitrooxy)ethoxy)phenoxy)ethyl 3-((2R)-2-amino-2-(methoxycarbonyl)ethylthio)-2-oxopropanoate;

4-(N-((1R)-1-(methoxycarbonyl)-2-(2-((2-(4-(2-(nitrooxy)ethoxy)phenoxy)ethyl)oxycarbonyl)-2-oxoethylthio)ethyl)carbamoyl)(2S)-2-aminobutanoic acid;

methyl (2*R*)-2-amino-3-((3-((3-((nitrooxy)methyl)benzyl)oxy)-2,3-dioxopropyl)thio) propanoate;

4-(N-((1R)-1-(methoxycarbonyl)-2-(2-(((3-((nitrooxy)methyl)phenyl)methyl)oxycarbonyl)-2-oxoethylthio)ethyl)carbamoyl)(2S)-2-aminobutanoic acid;

methyl (2*R*)-2-amino-3-((3-((4-((nitrooxy)methyl)benzyl)oxy)-2,3-dioxopropyl)thio) propanoate;

4-(N-((1R)-1-(methoxycarbonyl)-2-(2-(((4-((nitrooxy)methyl)phenyl)methyl)oxycarbonyl)-2-oxoethylthio)ethyl)carbamoyl)(2S)-2-aminobutanoic acid;

methyl (2*R*)-2-amino-3-((3-((3-(nitrooxy)propyl)amino)-2,3-dioxopropyl)thio)propanoate;

4-(N-((1R)-1-(methoxycarbonyl)-2-(2-(N-(3-(nitrooxy)propyl)carbamoyl)-2-oxoethylthio)ethyl)carbamoyl)(2S)-2-aminobutanoic acid;

methyl (2*R*)-2-amino-3-((3-((2,2-dimethyl-3-(nitrooxy)propyl)amino)-2,3-dioxopropyl)thio) propanoate;

4-(N-((1R)-2-(2-(N-(2,2-dimethyl-3-(nitrooxy)propyl)carbamoyl)-2-oxoethylthio)-1-(methoxycarbonyl)ethyl)carbamoyl)(2S)-2-aminobutanoic acid;

methyl (2*R*)-2-amino-3-((3-((2-(nitrooxy)-1-((nitrooxy)methyl)ethyl)amino)-2,3-dioxopropyl) thio)propanoate;

4-(N-((1R)-1-(methoxycarbonyl)-2-(2-(N-(2-(nitrooxy)-1-((nitrooxy)methyl)ethyl)carbamoyl)-2-oxoethylthio)ethyl)carbamoyl)(2S)-2-aminobutanoic acid;

methyl (2*R*)-2-amino-3-((3-(3-(nitrooxy)-2,2-bis((nitrooxy)methyl)propoxy)-2,3-dioxopropyl) thio)propanoate;

4-(N-((1R)-2-(2-((2,2-bis((nitrooxy)methyl)-3-(nitrooxy)propyl)oxycarbonyl)-2-oxoethylthio)-1-(methoxycarbonyl)ethyl)carbamoyl)(2S)-2-aminobutanoic acid;

methyl (2*R*)-2-amino-3-((3-(2-methyl-3-(nitrooxy)-2-((nitrooxy)methyl)propoxy)-2,3-dioxopropyl) thio)propanoate;

4-(N-((1R)-1-(methoxycarbonyl)-2-(2-((2-methyl-3-(nitrooxy)-2-((nitrooxy)methyl)propyl) oxycarbonyl)-2-oxoethylthio)ethyl)carbamoyl)(2S)-2-aminobutanoic acid;

methyl (2*R*)-2-amino-3-((3-(2-nitro-3-(nitrooxy)-2-((nitrooxy)methyl)propoxy)-2,3-dioxopropyl)thio)propanoate;

4-(N-((1R)-1-(methoxycarbonyl)-2-(2-((2-nitro-3-(nitrooxy)-2-((nitrooxy)methyl)propyl) oxycarbonyl)-2-oxoethylthio)ethyl)carbamoyl)(2S)-2-aminobutanoic acid;

methyl (2*R*)-2-amino-3-((3-(3-(nitrooxy)propoxy)-2,3-dioxopropyl)thio)propanoate;

4-(N-((1R)-1-(methoxycarbonyl)-2-(2-((3-(nitrooxy)propyl)oxycarbonyl)-2-oxoethylthio) ethyl)carbamoyl)(2S)-2-aminobutanoic acid;

methyl (2*R*)-2-amino-3-((3-(2,2-dimethyl-3-(nitrooxy)propoxy)-2,3-dioxopropyl)thio) propanoate;

4-(N-((1R)-2-(2-((2,2-dimethyl-3-(nitrooxy)propyl)oxycarbonyl)-2-oxoethylthio)-1-(methoxycarbonyl)ethyl)carbamoyl)(2S)-2-aminobutanoic acid;

methyl (2*R*)-2-amino-3-((3-(3-(nitrooxy)-2-((nitrooxy)methyl)propoxy)-2,3-dioxopropyl) thio)propanoate;

4-(N-((1R)-1-(methoxycarbonyl)-2-(2-((3-(nitrooxy)-2-((nitrooxy)methyl)propyl)oxycarbonyl)-2-oxoethylthio)ethyl)carbamoyl)(2S)-2-aminobutanoic acid;

methyl (2*R*)-2-amino-3-((3-(2-(nitrooxy)-1-((nitrooxy)methyl)ethoxy)-2,3-dioxopropyl)thio) propanoate;

4-(N-((1R)-1-(methoxycarbonyl)-2-(2-((2-(nitrooxy)-1-((nitrooxy)methyl)ethyl)oxycarbonyl)-2-oxoethylthio)ethyl)carbamoyl)(2S)-2-aminobutanoic acid;

methyl (2*R*)-2-amino-3-((3-((3,5-bis((nitrooxy)methyl)benzyl)oxy)-2,3-dioxopropyl)thio) propanoate;

4-(N-((1R)-2-(2-(((3,5-bis((nitrooxy)methyl)phenyl)methyl)oxycarbonyl)-2-oxoethylthio)-1-(methoxycarbonyl)ethyl)carbamoyl)(2S)-2-aminobutanoic acid;

methyl (2*R*)-2-(acetylamino)-3-((3-((2-(2-(nitrooxy)ethoxy)ethyl)amino)-2,3-dioxopropyl)thio) propanoate;

methyl (2*R*)-2-(acetylamino)-3-((3-((3-(nitrooxy)propyl)amino)-2,3-dioxopropyl)thio) propanoate;

2-(4-(2-(nitrooxy)ethoxy)phenoxy)ethyl 3-((2R)-2-(acetylamino)-2-(methoxycarbonyl) ethylthio)-2-oxopropanoate;

methyl (2*R*)-2-(acetylamino)-3-((3-((2,2-dimethyl-3-(nitrooxy)propyl)amino)-2,3-dioxopropyl)thio)propanoate;

methyl (2*R*)-2-(acetylamino)-3-((3-((3-((nitrooxy)methyl)benzyl)oxy)-2,3-dioxopropyl)thio) propanoate;

methyl (2*R*)-2-(acetylamino)-3-((3-((2-(nitrooxy)-1-((nitrooxy)methyl)ethyl)amino)-2,3-dioxopropyl)thio)propanoate;

methyl (2*R*)-2-(acetylamino)-3-((3-((4-((nitrooxy)methyl)benzyl)oxy)-2,3-dioxopropyl)thio) propanoate;

2,2-bis((nitrooxy)methyl)-3-(nitrooxy)propyl 3-((2R)-2-(acetylamino)-2-(methoxycarbonyl) ethylthio)-2-oxopropanoate;

2-methyl-3-(nitrooxy)-2-((nitrooxy)methyl)propyl 3-((2R)-2-(acetylamino)-2-(methoxycarbonyl) ethylthio)-2-oxopropanoate;

methyl (2*R*)-2-(acetylamino)-3-((3-(3-(nitrooxy)-2-((nitrooxy)methyl)propoxy)-2,3-dioxopropyl) thio)propanoate;

methyl (2*R*)-2-(acetylamino)-3-((3-(2-nitro-3-(nitrooxy)-2-((nitrooxy)methyl)propoxy)-2,3-dioxopropyl)thio)propanoate;

methyl (2*R*)-2-(acetylamino)-3-((3-(2-(nitrooxy)-1-((nitrooxy)methyl)ethoxy)-2,3-dioxopropyl) thio)propanoate;

methyl (2*R*)-2-(acetylamino)-3-((3-(3-(nitrooxy)propoxy)-2,3-dioxopropyl)thio)propanoate;

(3,5-bis((nitrooxy)methyl)phenyl)methyl 3-((2R)-2-(acetylamino)-2-(methoxycarbonyl) ethylthio)-2-oxopropanoate;

methyl (2*R*)-2-(acetylamino)-3-((3-(2,2-dimethyl-3-(nitrooxy)propoxy)-2,3-dioxopropyl) thio)propanoate;

4-((2-(((2R)-2,3-bis(nitrooxy)propyl)oxycarbonyl)(2S)-2-(2-oxopropanoylamino)ethyl) oxycarbonyl)(2S)-2-aminobutanoic acid;

(2S)-4-(((2S)-2-(((2S)-2,3-bis(nitrooxy)propyl)oxycarbonyl)-2-(2-oxopropanoylamino)ethyl) oxycarbonyl)-2-aminobutanoic acid;

4-(N-(4-(((2R)-2,3-bis(nitrooxy)propyl)oxycarbonyl)(4S)-4-(2-oxopropanoylamino)butyl) carbamoyl)(2S)-2-aminobutanoic acid;

(2S)-4-(N-((4S)-4-(((2S)-2,3-bis(nitrooxy)propyl)oxycarbonyl)-4-(2-oxopropanoylamino)butyl)

carbamoyl)-2-aminobutanoic acid;

4-(N-(5-(((2R)-2,3-bis(nitrooxy)propyl)oxycarbonyl)(5S)-5-(2-oxopropanoylamino) pentyl)carbamoyl)(2S)-2-aminobutanoic acid;

(2S)-4-(N-((5S)-5-(((2S)-2,3-bis(nitrooxy)propyl)oxycarbonyl)-5-(2-oxopropanoylamino)pentyl) carbamoyl)-2-aminobutanoic acid;

5-((2R)-2-(((2R)-2,3-bis(nitrooxy)propyl)oxycarbonyl)-2-(2-oxopropanoylamino)ethylthio)(2S)-2-amino-5-oxopentanoic acid;

5-((2R)-2-(((2S)-2,3-bis(nitrooxy)propyl)oxycarbonyl)-2-(2-oxopropanoylamino)ethylthio)(2S)-2-amino-5-oxopentanoic acid;

4-(N-(5-(N-((2R)-2,3-bis(nitrooxy)propyl)carbamoyl)(5S)-5-(2-oxopropanoylamino)pentyl) carbamoyl)(2S)-2-aminobutanoic acid;

(2S)-4-(N-((5S)-5-(N-((2S)-2,3-bis(nitrooxy)propyl)carbamoyl)-5-(2-oxopropanoylamino)pentyl) carbamoyl)-2-aminobutanoic acid;

(2S)-4-(N-((5S)-5-((2,2-bis((nitrooxy)methyl)-3-(nitrooxy)propyl)oxycarbonyl)-5-(2-oxopropanoylamino)pentyl)carbamoyl)-2-aminobutanoic acid;

(2S)-4-(N-((5S)-5-(((6S, 2R)-6-(nitrooxy)-4,8-dioxabicyclo(3.3.0)oct-2-yl)oxycarbonyl)-5-(2-oxopropanoylamino)pentyl)carbamoyl)-2-aminobutanoic acid;

(2S)-4-(N-((5S)-5-(((2S, 6R)-6-(nitrooxy)-4,8-dioxabicyclo(3.3.0)oct-2-yl)oxycarbonyl)-5-(2-oxopropanoylamino)pentyl)carbamoyl)-2-aminobutanoic acid;

4-(((1E)-2-(N-((2R)-2,3-bis(nitrooxy)propyl)carbamoyl)-1-azaprop-1-enyl)oxycarbonyl)(2S)-2-aminobutanoic acid;

4-(((1E)-2-(N-((2S)-2,3-bis(nitrooxy)propyl)carbamoyl)-1-azaprop-1-enyl)oxycarbonyl)(2S)-2-aminobutanoic acid;

4-(N-((1E)-2-(N-((2R)-2,3-bis(nitrooxy)propyl)carbamoyl)-1-azaprop-1-enyl)carbamoyl)(2S)-2-aminobutanoic acid;

4-(N-((1E)-2-(N-((2S)-2,3-bis(nitrooxy)propyl)carbamoyl)-1-azaprop-1-enyl)carbamoyl)(2S)-2-aminobutanoic acid;

4-(N-(1-(((2R)-2,3-bis(nitrooxy)propyl)oxycarbonyl)(1S)-5-(2-oxopropanoylamino)pentyl) carbamoyl)(2S)-2-aminobutanoic acid;

(2S)-4-(N-((1S)-1-(((2S)-2,3-bis(nitrooxy)propyl)oxycarbonyl)-5-(2-oxopropanoylamino)pentyl)

carbamoyl)-2-aminobutanoic acid;

4-(N-(1-(N-((2R)-2,3-bis(nitrooxy)propyl)carbamoyl)(1S)-5-(2-oxopropanoylamino)pentyl) carbamoyl)(2S)-2-aminobutanoic acid;

(2S)-4-(N-((1S)-1-(N-((2S)-2,3-bis(nitrooxy)propyl)carbamoyl)-5-(2-oxopropanoylamino)pentyl) carbamoyl)-2-aminobutanoic acid;

4-(N-(1-(((2R)-2,3-bis(nitrooxy)propyl)oxycarbonyl)(1S)-2-(2-oxopropanoyloxy)ethyl) carbamoyl)(2S)-2-aminobutanoic acid;

(2S)-4-(N-((1S)-1-(((2S)-2,3-bis(nitrooxy)propyl)oxycarbonyl)-2-(2-oxopropanoyloxy)ethyl) carbamoyl)-2-aminobutanoic acid;

4-(N-(1-(((2R)-2,3-bis(nitrooxy)propyl)oxycarbonyl)(1S)-4-(2-oxopropanoylamino) butyl)carbamoyl)(2S)-2-aminobutanoic acid;

(2S)-4-(N-((1S)-1-(((2S)-2,3-bis(nitrooxy)propyl)oxycarbonyl)-4-(2-oxopropanoylamino) butyl)carbamoyl)-2-aminobutanoic acid; or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention describes the metabolites of the nitrosated and/or nitrosylated pyruvate compounds and pharmaceutically acceptable salts thereof. These metabolites, include but are not limited to, the non-nitrosated and/or nitrosylated derivatives, degradation products, hydrolysis products, and the like, of the nitrosated and/or nitrosylated pyruvate compounds and pharmaceutically acceptable salts thereof.

Another embodiment of the invention provides processes for making the novel compounds of the invention and to the intermediates useful in such processes. The reactions are performed in solvents appropriate to the reagents and materials used are suitable for the transformations being effected. It is understood by one skilled in the art of organic synthesis that the functionality present in the molecule must be consistent with the chemical transformation proposed. This will, on occasion, necessitate judgment by the routineer as to the order of synthetic steps, protecting groups required, and deprotection conditions. Substituents on the starting materials may be incompatible with some of the reaction conditions required in some of the methods described, but alternative methods and substituents compatible with the reaction conditions will be readily apparent to one skilled in the art. The use of sulfur and oxygen protecting groups is well known for protecting thiol and alcohol groups against undesirable reactions during a synthetic procedure and many such protecting groups are known and described

by, for example, Greene and Wuts, *Protective Groups in Organic Synthesis*, Third Edition, John Wiley & Sons, New York (1999).

The chemical reactions described herein are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by one skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to one skilled in the art, *e.g.*, by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily prepared from known starting materials.

The compounds of Formulas (I) can be synthesized by one skilled in the art following the methods and examples described herein. The synthesis of the parent pyruvate compound (i.e. non-nitrosated and/or non-nitrosylated pyruvate compounds) are disclosed in, for example, U.S. Patent Nos. 5,120,737, 5,256,697, 5,876,916 and 6,455,542 and in WO 97/34856, WO 98/51277, WO 01/24793, WO 02/074301 and WO 02/090314 the disclosures of each of which are incorporated by reference herein in their entirety.

The pyruvate compounds are nitrosated and/or nitrosylated through one or more sites such as oxygen, sulfur and/or nitrogen using conventional methods known to one skilled in the art. For example, known methods for nitrosating and/or nitrosylating compounds are described in U.S. Patent Nos. 5,380,758, 5,859,053, 5,703,073 and 6,297,260; and in WO 94/03421, WO 94/04484, WO 94/12463, WO 95/09831, WO 95/19952, WO 95/30641, WO 97/27749, WO 98/19672, WO 98/21193, WO 00/51988, WO 00/61604, WO 00/72838, WO 01/00563, WO 01/04082, WO 01/10814, WO 01/12584, WO 01/45703, WO 00/61541, WO 00/61537, WO 02/11707, WO 02/30866 and in Oae et al, *Org. Prep. Proc. Int.*, *15*(3):165-198 (1983), the disclosures of each of which are incorporated by reference herein in their entirety. The methods of nitrosating and/or nitrosylating the compounds described in these references can be applied by one skilled in the art to produce any of the nitrosated and/or nitrosylated pyruvate compounds described herein. The nitrosated and/or nitrosylated pyruvate compounds of the invention

donate, transfer or release a biologically active form of nitrogen monoxide (i.e., nitric oxide).

Nitrogen monoxide can exist in three forms: NO- (nitroxyl), NO• (uncharged nitric oxide) and NO^+ (nitrosonium). NO• is a highly reactive short-lived species that is potentially toxic to cells. This is critical because the pharmacological efficacy of NO depends upon the form in which it is delivered. In contrast to the nitric oxide radical (NO•), nitrosonium (NO^+) does not react with O_2 or O_2^- species, and functionalities capable of transferring and/or releasing NO^+ and NO- are also resistant to decomposition in the presence of many redox metals. Consequently, administration of charged NO equivalents (positive and/or negative) is a more effective means of delivering a biologically active NO to the desired site of action.

Compounds contemplated for use in the invention, e.g., pyruvate compounds that are optionally nitrosated and/or nitrosylated through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation) and/or nitrogen, are, optionally, used in combination with nitric oxide and compounds that release nitric oxide or otherwise directly or indirectly deliver or transfer a biologically active form of nitrogen monoxide to a site of its intended activity, such as on a cell membrane *in vivo*.

The term "nitric oxide" encompasses uncharged nitric oxide (NO•) and charged nitrogen monoxide species, preferably charged nitrogen monoxide species, such as nitrosonium ion (NO^+) and nitroxyl ion (NO-). The reactive form of nitric oxide can be provided by gaseous nitric oxide. The nitrogen monoxide releasing, delivering or transferring compounds have the structure F-NO, wherein F is a nitrogen monoxide releasing, delivering or transferring moiety, and include any and all such compounds which provide nitrogen monoxide to its intended site of action in a form active for its intended purpose. The term "NO adducts" encompasses any nitrogen monoxide releasing, delivering or transferring compounds, including, for example, S-nitrosothiols, nitrites, nitrates, S-nitrothiols, sydnonimines, 2-hydroxy-2-nitrosohydrazines, (NONOates), (E)-alkyl-2-((E)- hydroxyimino)-5-nitro-3-hexeneamide (FK-409), (E)-alkyl-2-((E)-hydroxyimino)-5-nitro-3-hexeneamines, N-((2Z, 3E)-4-ethyl-2-(hydroxyimino)-6-methyl-5-nitro-3-heptenyl)-3-pyridinecarboxamide (FR 146801), nitrosoamines, furoxans as well as substrates for the endogenous enzymes which synthesize nitric oxide. NONOates include, but are not limited to, (Z)-1-(N-methyl-N-(6-(N-methyl-ammoniohexyl)amino))diazen-1-ium-1,2-diolate ("MAHMA/NO"), (Z)-1-(N-(3-ammoniopropyl)-N-(n-propyl)amino)diazen-1-ium-1,2-

diolate ("PAPA/NO"), (Z)-1-(N-(3-aminopropyl)-N-(4-(3-aminopropylammonio)butyl)-amino) diazen-1-ium-1,2-diolate (spermine NONOate or "SPER/NO") and sodium(Z)-1-(N,N-diethylamino)diazenium-1,2-diolate (diethylamine NONOate or "DEA/NO") and derivatives thereof. NONOates are also described in U.S. Patent Nos. 6,232,336, 5,910,316 and 5,650,447, the disclosures of which are incorporated herein by reference in their entirety. The "NO adducts" can be mono-nitrosylated, poly-nitrosylated, mono-nitrosated and/or poly-nitrosated at a variety of naturally susceptible or artificially provided binding sites for biologically active forms of nitrogen monoxide.

One group of NO adducts is the S-nitrosothiols, which are compounds that include at least one -S-NO group. These compounds include S-nitroso-polypeptides (the term "polypeptide" includes proteins and polyamino acids that do not possess an ascertained biological function, and derivatives thereof); S-nitrosylated amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures and derivatives thereof); S-nitrosylated sugars; S-nitrosylated, modified and unmodified, oligonucleotides (preferably of at least 5, and more preferably 5-200 nucleotides); straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted S-nitrosylated hydrocarbons; and S-nitroso heterocyclic compounds. S-nitrosothiols and methods for preparing them are described in U.S. Patent Nos. 5,380,758 and 5,703,073; WO 97/27749; WO 98/19672; and Oae et al, *Org. Prep. Proc. Int.*, *15*(3):165-198 (1983), the disclosures of each of which are incorporated by reference herein in their entirety.

Another embodiment of the invention is S-nitroso amino acids where the nitroso group is linked to a sulfur group of a sulfur-containing amino acid or derivative thereof. Such compounds include, for example, S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine, S-nitroso-glutathione, S-nitroso-cysteinyl-glycine, and the like.

Suitable S-nitrosylated proteins include thiol-containing proteins (where the NO group is attached to one or more sulfur groups on an amino acid or amino acid derivative thereof) from various functional classes including enzymes, such as tissue-type plasminogen activator (TPA) and cathepsin B; transport proteins, such as lipoproteins; heme proteins, such as hemoglobin and serum albumin; and biologically protective proteins, such as immunoglobulins, antibodies and

cytokines. Such nitrosylated proteins are described in WO 93/09806, the disclosure of which is incorporated by reference herein in its entirety. Examples include polynitrosylated albumin where one or more thiol or other nucleophilic centers in the protein are modified.

Other examples of suitable S-nitrosothiols include:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; or

(iii) $H_2N\text{-}CH(CO_2H)\text{-}(CH_2)_m\text{-}C(O)NH\text{-}CH(CH_2SNO)\text{-}C(O)NH\text{-}CH_2\text{-}CO_2H$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring. a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, an arylsulfonyloxy, a urea, a nitro, -T-Q-, or $-(C(R_g)(R_h))_k\text{-}T\text{-}Q$ or R_e and R_f taken together are an oxo, a methanthial, a heterocyclic ring, a cycloalkyl group, an oxime, a hydrazone or a bridged cycloalkyl group; Q is -NO or $-NO_2$; and T is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o-$ or $-N(R_a)R_i$, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyloxy, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, $-CH_2\text{-}C(T\text{-}Q)(R_g)(R_h)$, or $-(N_2O_2\text{-})^-\bullet M^+$, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is $-CH_2\text{-}C(T\text{-}Q)(R_g)(R_h)$ or $-(N_2O_2\text{-})\bullet M^+$; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group; and

R_g and R_h at each occurrence are independently R_e.

In cases where R_e and R_f are a heterocyclic ring or taken together R_e and R_f are a

heterocyclic ring, then R_i can be a substituent on any disubstituted nitrogen contained within the radical wherein R_i is as defined herein.

Nitrosothiols can be prepared by various methods of synthesis. In general, the thiol precursor is prepared first, then converted to the S-nitrosothiol derivative by nitrosation of the thiol group with $NaNO_2$ under acidic conditions (pH is about 2.5) which yields the S-nitroso derivative. Acids which can be used for this purpose include aqueous sulfuric, acetic and hydrochloric acids. The thiol precursor can also be nitrosylated by reaction with an organic nitrite such as tert-butyl nitrite, or a nitrosonium salt such as nitrosonium tetrafluoroborate in an inert solvent.

Another group of NO adducts for use in the invention, where the NO adduct is a compound that donates, transfers or releases nitric oxide, include compounds comprising at least one ON-O- or ON-N- group. The compounds that include at least one ON-O- or ON-N- group are preferably ON-O- or ON-N-polypeptides (the term "polypeptide" includes proteins and polyamino acids that do not possess an ascertained biological function, and derivatives thereof); ON-O- or ON-N-amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); ON-O- or ON-N-sugars; ON-O- or -ON-N- modified or unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); ON-O- or ON-N- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and ON-O-, ON-N- or ON-C-heterocyclic compounds.

Another group of NO adducts for use in the invention include nitrates that donate, transfer or release nitric oxide, such as compounds comprising at least one O_2N-O-, O_2N-N- or O_2N-S- group. Preferred among these compounds are O_2N-O-, O_2N-N- or O_2N-S- polypeptides (the term "polypeptide" includes proteins and also polyamino acids that do not possess an ascertained biological function, and derivatives thereof); O_2N-O-, O_2N-N- or O_2N-S- amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); O_2N-O-, O_2N-N- or O_2N-S- sugars; O_2N-O-, O_2N-N- or O_2N-S- modified and unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); O_2N-O-, O_2N-N- or O_2N-S- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and O_2N-O-, O_2N-N- or O_2N-S- heterocyclic compounds. Preferred examples of compounds comprising at least one O_2N-O-, O_2N-N- or

O_2N-S- group include isosorbide dinitrate, isosorbide mononitrate, clonitrate, erythrityl tetranitrate, mannitol hexanitrate, nitroglycerin, pentaerythritoltetranitrate, pentrinitrol, propatylnitrate and organic nitrates with a sulfhydryl-containing amino acid such as, for example SPM 3672, SPM 5185, SPM 5186 and those disclosed in U. S. Patent Nos. 5,284,872, 5,428,061, 5,661,129, 5,807,847 and 5,883,122 and in WO 97/46521, WO 00/54756 and in WO 03/013432, the disclosures of each of which are incorporated by reference herein in their entirety.

Another group of NO adducts are N-oxo-N-nitrosoamines that donate, transfer or release nitric oxide and are represented by the formula: $R^{1"}R^{2"}N$-$N(O$-$M^+)$-NO, where $R^{1"}$ and $R^{2"}$ are each independently a polypeptide, an amino acid, a sugar, a modified or unmodified oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and where M^+ is an organic or inorganic cation, such as, for example, an alkyl substituted ammonium cation or a Group I metal cation.

The invention is also directed to compounds that stimulate endogenous NO or elevate levels of endogenous endothelium-derived relaxing factor (EDRF) *in vivo* or are substrates for nitric oxide synthase. Such compounds include, for example, L-arginine, L-homoarginine, and N-hydroxy-L-arginine, including their nitrosated and/or nitrosylated analogs (e.g., nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, nitrosated L-homoarginine and nitrosylated L-homoarginine), precursors of L-arginine and/or physiologically acceptable salts thereof, including, for example, citrulline, ornithine, glutamine, lysine, polypeptides comprising at least one of these amino acids, inhibitors of the enzyme arginase (e.g., N-hydroxy-L-arginine and 2(S)-amino-6-boronohexanoic acid), nitric oxide mediators and/or physiologically acceptable salts thereof, including, for example, pyruvate, pyruvate precursors, α-keto acids having four or more carbon atoms, precursors of α-keto acids having four or more carbon atoms (as disclosed in WO 03/017996, the disclosure of which is incorporated herein in its entirety), and the substrates for nitric oxide synthase, cytokines, adenosin, bradykinin, calreticulin, bisacodyl, and phenolphthalein. EDRF is a vascular relaxing factor secreted by the endothelium, and has been identified as nitric oxide (NO) or a closely related derivative thereof (Palmer et al, *Nature*, 327:524-526 (1987); Ignarro et al, *Proc. Natl. Acad. Sci. USA*, 84:9265-9269 (1987)).

The invention is also based on the discovery that compounds and compositions of the

invention may be used in conjunction with other therapeutic agents for co-therapies, partially or completely, in place of other therapeutic agents, such as, for example, aldosterone antagonists, alpha-adrenergic receptor antagonists, antidiabetic compounds, anti-hyperlipidemic drugs, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antioxidants, antithrombotic and vasodilator drugs, beta-adrenergic blockers, calcium channel blockers, diuretics, endothelin antagonists, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and mixtures of two or more thereof. The therapeutic agent may optionally be nitrosated and/or nitrosylated.

Suitable aldosterone antagonists include, but are not limited to, canrenone, potassium canrenoate, spironolactone, eplerenone, and the like. Suitable aldosterone antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable alpha-adrenergic receptor antagonists include but are not limited to, phentolamine, tolazoline, idazoxan, deriglidole, RX 821002, BRL 44408, BRL 44409, BAM 1303, labetelol, ifenprodil, rauwolscine, corynathine, raubascine, tetrahydroalstonine, apoyohimbine, akuammigine, β-yohimbine, yohimbol, yohimbine, pseudoyohimbine, epi-3α-yohimbine, 10-hydroxy-yohimbine, 11-hydroxy-yohimbine, tamsulosin, benoxathian, atipamezole, BE 2254, WB 4101, HU-723, tedisamil, mirtazipine, setiptiline, reboxitine, delequamine, naftopil, saterinone, SL 89.0591, ARC 239, urapidil, 5-methylurapidil, monatepi, haloperidol, indoramin, SB 216469, moxisylyte, trazodone, dapiprozole, efaroxan, Recordati 15/2739, SNAP 1069, SNAP 5089, SNAP 5272, RS 17053, SL 89.0591, KMD 3213, spiperone, AH 11110A, chloroethylclonidine, BMY 7378, niguldipine, and the like. Suitable alpha-adrenergic receptor antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable antidiabetic compounds include but are not limited to, acarbose, acetohexamide,

buformin, carbutamide, chlorpropamide, glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glisoxepid, glyburide, glybuthiazol(e), glybuzole, glyhexamide, glymidine, glypinamide, insulin, metformin, miglitol, nateglinide, phenbutamide, phenformin, pioglitazone, repaglinide, rosiglitazone, tolazamide, tolbutamide, tolcyclamide, troglitazone, voglibose, and the like. Suitable antidiabetic compounds are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable anti-hyperlipidemic drugs include, but are not limited to, statins or HMG-CoA reductase inhibitors, such as, for example, atorvastatin (LIPITOR®), bervastatin, cerivastatin (BAYCOL®), fluindostatin (Sandoz XU-62-320), fluvastatin, lovastatin (MEVACOR®), mevastatin, privastatin (PRAVACHOL®), rosuvastatin, simvastatin (ZOCOR®), velostatin (also known as synvinolin) and the like; gemfibrozil, cholystyramine, colestipol, nicotinic acid, bile acid sequestrants, such as, for example, cholestyramine, colesevelam, colestipol, poly(methyl-(3-trimethylaminopropyl) imino-trimethylene dihalide) and the like; probucol; fibric acid agents or fibrates, such as, for example, bezafibrate (Bezalip™), beclobrate, binifibrate, ciprofibrate, clinofibrate, clofibrate, etofibrate, fenofibrate (Lipidil™, Lipidil Micro™), gemfibrozil (Lopid™.), nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate and the like. Suitable anti-hyperlipidemic drugs are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable angiotensin II antagonists include, but are not limited to, angiotensin, candesartan, cilexetil, eprosartan, irbesartan, losartan, olmesartan, medoxomil, remikirin, riposartan, saralasin, tasosartan, telmisartan, valsartan, zolasartin, BMS 184698, 3-(2'(tetrazole-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo(4,5-b)pyridine, antibodies to angiotensin II, BAY106734, BIBR363, BMS184698, CGP42112A, CGP49870, CP148130, CL329167, DuP 753, E4177, E4188, EMD66397, EMD73495, EMD66684, EXP-3174, EXP 7711, EXP9954, FR1153332, GA0050, GA0056, HN65021, HOE720, HR720, KT3579, LF70156. LRB057, LRB081, LY266099, LY301875, ME3221, MK 954, PD123177, PD126055, SC51757, SC54629, SC52458, SL910102, TAK536, UP2696, U96849, UK77778, WAY126227,

WK1260, WK1492, YH1498, YM 358, YM31472, and the like. Suitable angiotensin II antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable angiotensin-converting enzyme inhibitors (ACE inhibitors) include, but are not limited to, alacepril, benazepril, benazeprilat, captopril, ceronapril, cilazapril, delapril, duinapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, moveltipril, moexipril, naphthopidil, pentopril, perindopril, quinapril, ramipril, rentipril, spirapril, temocapril, trandolapril, urapidil, zofenopril, acylmercapto and mercaptoalkanoyl pralines, carboxyalkyl dipeptides, carboxyalkyl dipeptide, phosphinylalkanoyl pralines, and the like. Suitable ACE inhibitors are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Sutiable antioxidants include, but are not limited to, small-molecule antioxidants and antioxidant enzymes. Suitable small-molecule antioxidants include, but are not limited to, hydralazine compounds, glutathione, vitamin C, vitamin E, cysteine, N-acetyl-cysteine, β-carotene, ubiquinone, ubiquinol-10, tocopherols, coenzyme Q, superoxide dismutase mimetics and the like. Suitable antioxidant enzymes include, but are not limited to, superoxide dismutase, catalase, glutathione peroxidase, and the like. The antioxidant enzymes can be delivered by gene therapy as a viral vertor and/or a non-viral vector. Suitable antioxidants are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable antithrombotic and vasodilator drugs include, but are not limited to, acetorphan, acetylsalicylic acid, argatroban, bamethan, benfurodil, benziodarone, betahistine, brovincamine, bufeniode, citicoline, clobenfurol, clopidogrel, cyclandelate, dalteparin, dipyridamol, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isobogrel, isoxsuprine, heparin, lamifiban, midrodine, nadroparin, nicotinoyl alcohol, nylidrin, ozagrel, perhexiline, phenylpropanolamine, prenylamine, papaveroline, reviparin sodium salt, ridogrel, suloctidil, tinofedrine, tinzaparin, trifusal, xanthinal niacinate, and the like. Suitable

antithrombotic and vasodilator drugs are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable beta-adrenergic blockers include, but are not limited to, acebutolol, alprenolol, amosulalol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucindolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butafilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cindolol, cloranolol, dilevalol, epanolol, esmolol, indenolol, labetalol, landiolol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol, nipradilol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, xibenolol, and the like. Suitable beta-adrenergic blockers are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable calcium channel blockers include, but are not limited to, amlodipine, aranidipine, barnidipine, benidipine, bepridil, cilnidipine, cinnarizine, clentiazem, diltiazen, dotarizine, efonidipine, elgodipine, fantofarone, felodipine, flunarizine, fluspirilene, gallopamil, isradipine, lacidipine, lercanidipine, lomerizine, manidipine, mibefradil, monatepil, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, semotiadil, veraparmil, and the like. Suitable calcium channel blockers are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable diuretics include but are not limited to, thiazides (such as, for example, althiazide, bendroflumethiazide, benzclortriazide, benzthiazide, buthiazide, chlorothiazide, cyclopenethiazide, cyclothiazide, ethiazide, hydrochlorothiazide, methyclothiazide, penflutazide, polythiazide, teclothiazide, trichlormethiazide, triflumethazide, and the like); ambuside, amiloride, aminometradine, azosemide, bemetizide, bumetanide, butazolamide, butizide, ethacrynic acid, canrenone, chloraminophenamide, chlorazanil, chlormerodrin,

chlorthalidone, clofenamide, clopamide, clorexolone, disulfamide, ethacrynic acid, ethoxzolamide, etozolon, fenquizone, furosemide, mefruside, meralluride, mercaptomerin sodium, mercumallylic acid, mersalyl, methazolamide, metolazone, muzolimine, pamabrom, paraflutizide, piretanide, protheobromine, quinethazone, scoparius, spironalactone, theobromine, ticrynafen, torsemide, triamterene, xipamide or potassium, and the like. Suitable diuretics are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable endothelin antagonists include, but are not limited to, bosentan, endothelin, sulfonamide endothelin antagonists, BQ-123, SQ 28608, and the like. Suitable endothelin antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable H_2 receptor anatgonists include, but are not limited to, burimamide, cimetidine, ebrotidin, famotidine, nizatidine, roxatidine, rantidine, tiotidine, and the like. Suitable H_2 receptor antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995, Pgs. 901-915; the Merck Index on CD-ROM, 13th Edition; and on STN Express, file phar and file registry; and in WO 00/28988 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety.

Suitable neutral endopeptidase inhibitors include, but are not limited to, atrial natriuretic peptides, diazapins, azepinones, ecadotril, omapatrilat, sampatrilat, BMS 189,921, and the like. Neutral endopeptidase inhibitors are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable NSAIDs include, but are not limited to, acetaminophen, acemetacin, aceclofenac, alminoprofen, amfenac, bendazac, benoxaprofen, bromfenac, bucloxic acid, butibufen, carprofen, cinmetacin, clopirac, diclofenac, etodolac, felbinac, fenclozic acid, fenbufen, fenoprofen, fentiazac, flunoxaprofen, flurbiprofen, ibufenac, ibuprofen, indomethacin, isofezolac, isoxepac,

indoprofen, ketoprofen, lonazolac, loxoprofen, metiazinic acid, mofezolac, miroprofen, naproxen, oxaprozin, pirozolac, pirprofen, pranoprofen, protizinic acid, salicylamide, sulindac, suprofen, suxibuzone, tiaprofenic acid, tolmetin, xenbucin, ximoprofen, zaltoprofen, zomepirac, aspirin, acemetcin, bumadizon, carprofenac, clidanac, diflunisal, enfenamic acid, fendosal, flufenamic acid, flunixin, gentisic acid, ketorolac, meclofenamic acid, mefenamic acid, mesalamine, prodrugs thereof, and the like. Suitable NSAIDs are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995, Pgs. 617-657; the Merck Index on CD-ROM, 13th Edition; and on STN Express, file phar and file registry; and in U.S. Patent Nos. 6,057,347 and 6,297,260 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety.

Suitable potassium channel blockers include but are not limited to, nicorandil, pinacidil, cromakalim (BRL 34915), aprikalim, bimakalim, emakalim, lemakalim, minoxidil, diazoxide, 9-chloro-7-(2-chlorophenyl)-5H-pyrimido(5,4,-d)(2)-benzazepine, Ribi, CPG-11952, CGS-9896, ZD 6169, diazixide, Bay X 9227, P1075, Bay X 9228, SDZ PCO 400, WAY-120,491, WAY-120,129, Ro 31-6930, SR 44869, BRL 38226, S 0121, SR 46142A, CGP 42500, SR 44994, artilide fumarate, lorazepam, temazepam, rilmazafone, nimetazepam, midazolam, lormetazepam, loprazolam, ibutilide fumarate, haloxazolam, flunitrazepam, estazolam, doxefazepam, clonazepam, cinolazepam, brotizolam, and the like. Suitable potassium channel blockers are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable platelet reducing agents include but are not limited to, fibrinolytic agents such as for example, ancrod, anistreplase, bisobrin lactate, brinolase, Hageman factor (i.e. factor XII) fragments, molsidomine, plasminogen activators such as, for example, streptokinase, tissue plasminogen activators (TPA), urokinase, pro-Urokinase, recombinant TPA, plasmin, plasminogen, and the like; anti-coagulant agents including but are not limited to, inhibitors of factor Xa, factor TFPI, factor VIIa, factor IXc, factor Va, factor VIIIa, inhibitors of other coagulation factors, and the like; vitamin K antagonists, such as, for example, coumarin, coumarin derivatives (e.g., warfarin sodium); glycosoaminoglycans such as, for example,

heparins both in unfractionated form and in low molecular weight form; ardeparin sodium, bivalirudin, bromindione, coumarin, dalteparin sodium, danaparoid sodium; dazoxiben hydrochloride, desirudin, dicumarol, efegatran sulfate, enoxaparin sodium, ifetroban, ifetroban sodium, lyapolate sodium, nafamostat mesylate, phenprocoumon, sulfatide, tinzaparin sodium, retaplase; trifenagrel, warfarin, dextrans and the like; acadesine, anipamil, argatroban, aspirin, clopidogrel, diadenosine 5',5'''-P1,P4-tetraphosphate (Ap4A) analogs, difibrotide, dilazep dihydrochloride, dipyridamole, dopamine, 3-methoxytyramine, glucagon, glycoprotein IIb/IIIa antagonists, such as, for example, Ro-43-8857, L-700,462, iloprost, isocarbacyclin methyl ester, itazigrel, ketanserin, BM-13.177, lamifiban, lifarizine, molsidomine, nifedipine, oxagrelate, prostaglandins, platelet activating factor antagonists such as, for example, lexipafant, prostacyclins, pyrazines, pyridinol carbamate, ReoPro (i.e., abciximab), sulfinpyrazone, synthetic compounds BN-50727, BN-52021, CV-4151, E-5510, FK-409, GU-7, KB-2796, KBT-3022, KC-404, KF-4939, OP-41483, TRK-100, TA-3090, TFC-612, ZK-36374, 2,4,5,7-tetrathiaoctane, 2,4,5,7-tetrathiaoctane 2,2-dioxide, 2,4,5-trithiahexane, theophyllin pentoxifyllin, thromboxane and thromboxane synthetase inhibitors such as, for example, picotamide, sulotroban, ticlopidine, tirofiban, trapidil, ticlopidine, trifenagrel, trilinolein, 3-substituted 5,6-bis(4-methoxyphenyl)-1,2,4-triazines; antibodies to glycoprotein IIb/IIIa; anti-serotonin drugs, such as, for example, clopridogrel; sulfinpyrazone and the like; aspirin; dipyridamole; clofibrate; pyridinol carbamate; glucagon, caffeine; theophyllin pentoxifyllin; ticlopidine, and the like. Suitable platelet reducing agents are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable proton pump inhibitors include, but are not limited to, omeprazole, lansoprazole, pantoprazole, rabeprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, esomeprazole, 2-(2-benzimidazolyl)-pyridine, tricyclic imidazole, thienopydidine benzimidazole, fluoroalkoxy substituted benzimidazole, dialkoxy benzimidazole, N-substituted 2-(pyridylalkenesulfinyl) benzimidazole, cycloheptenepyridine, 5-pyrrolyl-2-pyridylmethylsulfinyl benzimidazole, alkylsulfinyl benzimidazole, fluoro-pyridylmethylsulfinyl benzimidazole, imidazo(4,5-b)pydridine, RO 18-5362, IY 81149, 4-amino-3-carbonyl quinoline, 4-amino-3-acylnaphthyride, 4-aminoquinoline, 4-amino-3-acylquinoline, 3-butyryl-4-(2-

methylphenylamino)-8-(2-hydroxyethoxy)quinoline, quinazoline, tetrahydroisoquinolin-2-yl pyrimidine, YH 1885, 3-substituted 1,2,4-thiadiazolo(4,5-a) benzimidazole, 3-substituted imidazo(1,2-d)-thiadiazole, 2-sulfinylnicotinamide, pyridylsulfinylbenz imidazole, pyridylsulfinyl thieno imidazole, theinoimidazole-toluidine, 4,5-dihydrooxazole, thienoimidazole-toluidine, Hoe-731, imidazo(1,2-a)pyridine, pyrrolo(2,3-b)pyridine,.and the like. Suitable proton pump inhibitors are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; the Merck Index on CD-ROM, 13th Edition; and on STN Express, file phar and file registry; and in WO 00/50037 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety.

Suitable renin inhibitors include, but are not limited to, aldosterone, enalkrein, medullipin, tonin, RO 42-5892, A 65317, CP 80794, ES 1005, ES 8891, SQ 34017, urea derivatives of peptides, amino acids connected by nonpeptide bonds, di- and tri-peptide derivatives, amino acids and derivatives thereof, diol sulfonamides and sulfinyls, modified peptides, peptidyl beta-aminoacyl aminodiol carbamates, monoclonal antibodies to rennin, and the like. Suitable renin inhibitors are described more fully in U.S. Patent Nos. 5,116,835, 5,114,937, 5,106,835, 5,104,869, 5,095,119, 5,098,924), 5,095,006, 5,089,471, 5,075,451, 5,066,643, 5,063,208, 4,845,079, 5,055,466, 4,980,283, 4,885,292), 4,780,401, 5,071,837, 5,064,965, 5,063,207, 5,036,054, 5,036,053, 5,034,512, and 4,894,437, the disclosures of each of which are incorporated herein by reference in their entirety; and in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable COX-2 inhibitors include, but are not limited to, NS-386, nimesulide, flosulide, celecoxib, rofecoxib, COX-189, etoracoxib, valdecoxib, Bextra, Dynastat, Arcoxia, SC-57666, DuP 697, GW-406381, SC-58125, SC-58635, and the like, and mixtures of two or more thereof. Suitable COX-2 inhibitors are in U.S. Patent Nos. 5,344,991, 5,380,738, 5,393,790, 5,409,944, 5,434,178, 5,436,265, 5,466,823, 5,474,995, 5,510,368, 5,536,752, 5,550,142, 5,552,422, 5,604,253, 5,604,260, and 5,639,780 and in WO 94/03387, WO 94/15723, WO 94/20480, WO 94/26731, WO 94/27980, WO 95/00501, WO 95/15316, WO 96/03387, WO 96/03388, WO

96/06840, WO 96/21667, WO 96/31509, WO 96/36623, WO 97/14691, WO 97/16435, WO 01/45703 and WO 01/87343, the disclosures of each of which are incorporated herein by reference in their entirety; and in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Another embodiment of the invention provides methods for methods for the treatment of diseases resulting from oxidative stress, diabetes, reperfusion injury following ischemia, and the methods for the preservation of tissues, organs, organ parts and/or limbs comprising administering to the patient in need thereof a therapeutically effective amount of the compounds and/or compositions described herein. For example, the patient can be administered a therapeutically effective amount of at least one nitrosated and/or nitrosylated pyruvate compound. In another embodiment, the patient can be administered a therapeutically effective amount of at least one pyruvate compound, that is optionally nitrosated and/or nitrosylated, and at least one compound that donates, transfers or releases nitric oxide, or elevates levels of endogenous EDRF or nitric oxide, or is a substrate for nitric oxide synthase. In yet another embodiment, the patient can be administered a therapeutically effective amount of at least one pyruvate compound, that is optionally nitrosated and/or nitrosylated, and at least one therapeutic agent, including but not limited to, such as, for example, aldosterone antagonists, alpha-adrenergic receptor antagonists, antidiabetic compounds, anti-hyperlipidemic drugs, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antioxidants, antithrombotic and vasodilator drugs, beta-adrenergic blockers, calcium channel blockers, diuretics, endothelin antagonists, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and, optionally, at least one compound that donates, transfers or releases nitric oxide, or elevates levels of endogenous EDRF or nitric oxide, or is a substrate for nitric oxide synthase. The compounds can be administered separately or in the form of a composition.

The compounds can be administered separately or in the form of a composition. When administered separately, the pyruvate compound, that is optionally nitrosated and/or

nitrosylated, nitric oxide donor and/or therapeutic agent can be administered about the same time as part of the overall treatment regimen, i.e., as a combination therapy. "About the same time" includes administering the nitrosated and/or nitrosylated pyruvate compound simultaneously, sequentially, at the same time, at different times on the same day, or on different days, as long as they are administered as part of an overall treatment regimen, i.e., combination therapy or a therapeutic cocktail.

When administered in vivo, the compounds and compositions of the invention can be administered in combination with pharmaceutically acceptable carriers and in dosages described herein. When the compounds and compositions of the invention are administered as a combination of at least one pyruvate compound and/or at least one nitrosated and/or nitrosylated pyruvate compound and/or at least one nitric oxide donor and/or therapeutic agent, they can also be used in combination with one or more additional compounds which are known to be effective against the specific disease state targeted for treatment. The nitric oxide donors, therapeutic agents and/or other additional compounds can be administered simultaneously with, subsequently to, or prior to administration of the nitrosated and/or nitrosylated pyruvate compound.

The compounds and compositions of the invention can be administered by any available and effective delivery system including, but not limited to, orally, bucally, parenterally, by inhalation spray, by topical application, by injection, transdermally, or rectally (e.g., by the use of suppositories) in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles, as desired. Parenteral includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques. In a preferred embodiment the nitrosated and/or nitrosylated pyruvate compound are administered parenterally.

Transdermal compound administration, which is known to one skilled in the art, involves the delivery of pharmaceutical compounds via percutaneous passage of the compound into the systemic circulation of the patient. Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. Other components can be incorporated into the transdermal patches as well. For example, compositions and/or transdermal patches can be formulated with one or more preservatives or bacteriostatic agents including, but not limited to, methyl hydroxybenzoate, propyl

hydroxybenzoate, chlorocresol, benzalkonium chloride, and the like. Dosage forms for topical administration of the compounds and compositions can include creams, sprays, lotions, gels, ointments, eye drops, nose drops, ear drops, and the like. In such dosage forms, the compositions of the invention can be mixed to form white, smooth, homogeneous, opaque cream or lotion with, for example, benzyl alcohol 1% or 2% (wt/wt) as a preservative, emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water and sorbitol solution. In addition, the compositions can contain polyethylene glycol 400. They can be mixed to form ointments with, for example, benzyl alcohol 2% (wt/wt) as preservative, white petrolatum, emulsifying wax, and tenox II (butylated hydroxyanisole, propyl gallate, citric acid, propylene glycol). Woven pads or rolls of bandaging material, e.g., gauze, can be impregnated with the compositions in solution, lotion, cream, ointment or other such form can also be used for topical application. The compositions can also be applied topically using a transdermal system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated with the composition and laminated to an impermeable backing.

The compositions can also be applied topically using a transdermal system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated with the composition and laminated to an impermeable backing. In a particular embodiment, the compositions of the invention are administered as a transdermal patch, more particularly as a sustained-release transdermal patch. The transdermal patches of the invention can include any conventional form such as, for example, adhesive matrix, polymeric matrix, reservoir patch, matrix or monolithic-type laminated structure, and are generally comprised of one or more backing layers, adhesives, penetration enhancers, an optional rate controlling membrane and a release liner which is removed to expose the adhesives prior to application. Polymeric matrix patches also comprise a polymeric-matrix forming material. Suitable transdermal patches are described in more detail in, for example, U. S. Patent Nos. 5,262,165, 5,948,433, 6,010,715 and 6,071,531, the disclosure of each of which are incorporated herein in their entirety.

Solid dosage forms for oral administration can include capsules, sustained-release capsules, tablets, sustained release tablets, chewable tablets, sublingual tablets, effervescent tablets, pills, powders, granules and gels. In such solid dosage forms, the active compounds can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms

can also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, effervescent tablets, and pills, the dosage forms can also comprise buffering agents. Soft gelatin capsules can be prepared to contain a mixture of the active compounds or compositions of the invention and vegetable oil. Hard gelatin capsules can contain granules of the active compound in combination with a solid, pulverulent carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives of gelatin. Tablets and pills can be prepared with enteric coatings.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Suppositories for vaginal or rectal administration of the compounds and compositions of the invention, such as for treating pediatric fever and the like, can be prepared by mixing the compounds or compositions with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at room temperature but liquid at rectal temperature, such that they will melt in the rectum and release the drug.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing agents, wetting agents and/or suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be used are water, Ringer's solution, and isotonic sodium chloride solution. Sterile fixed oils are also conventionally used as a solvent or suspending medium.

The compositions of this invention can further include conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include, for example, water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, surfactants, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides,

petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, and the like. The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds. For parenteral application, particularly suitable vehicles consist of solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants. Aqueous suspensions may contain substances which increase the viscosity of the suspension and include, for example, sodium carboxymethyl cellulose, sorbitol and/or dextran. Optionally, the suspension may also contain stabilizers.

The composition, if desired, can also contain minor amounts of wetting agents, emulsifying agents and/or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulations can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like.

Various delivery systems are known and can be used to administer the compounds or compositions of the invention, including, for example, encapsulation in liposomes, microbubbles, emulsions, microparticles, microcapsules and the like. The required dosage can be administered as a single unit or in a sustained release form.

The bioavailabilty of the compositions can be enhanced by micronization of the formulations using conventional techniques such as grinding, milling, spray drying and the like in the presence of suitable excipients or agents such as phospholipids or surfactants.

Sustained release dosage forms of the invention may comprise microparticles and/or nanoparticles having a therapeutic agent dispersed therein or may comprise the therapeutic agent in pure, preferably crystalline, solid form. For sustained release administration, microparticle dosage forms comprising pure, preferably crystalline, therapeutic agents are preferred. The therapeutic dosage forms of this aspect of the invention may be of any configuration suitable for sustained release.

Nanoparticle sustained release therapeutic dosage forms are preferably biodegradable

and, optionally, bind to the vascular smooth muscle cells and enter those cells, primarily by endocytosis. The biodegradation of the nanoparticles occurs over time (e.g., 30 to 120 days; or 10 to 21 days) in prelysosomic vesicles and lysosomes. Preferred larger microparticle therapeutic dosage forms of the invention release the therapeutic agents for subsequent target cell uptake with only a few of the smaller microparticles entering the cell by phagocytosis. A practitioner in the art will appreciate that the precise mechanism by which a target cell assimilates and metabolizes a dosage form of the invention depends on the morphology, physiology and metabolic processes of those cells. The size of the particle sustained release therapeutic dosage forms is also important with respect to the mode of cellular assimilation. For example, the smaller nanoparticles can flow with the interstitial fluid between cells and penetrate the infused tissue. The larger microparticles tend to be more easily trapped interstitially in the infused primary tissue, and thus are useful to deliver anti-proliferative therapeutic agents.

Particular sustained release dosage forms of the invention comprise biodegradable microparticles or nanoparticles. More particularly, biodegradable microparticles or nanoparticles are formed of a polymer containing matrix that biodegrades by random, nonenzymatic, hydrolytic scissioning to release therapeutic agent, thereby forming pores within the particulate structure.

In a particular embodiment, the compositions of the invention are administered parenterally or orally as a sustained release tablet or a sustained release capsule. For example, the parental or sustained release formulations can comprise a therapeutically effective amount of at least one nitrosated and/or nitrosylated pyruvate compound or a pharmaceutically acceptable salt thereof, and, optionally at least one nitric oxide donor, or the parental or sustained release formulations can comprise a therapeutically effective amount of at least one nitrosated and/or nitrosylated cardiovascular compound or a pharmaceutically acceptable salt thereof, and at least one nitric oxide donor, and, optionally at least one therapeutic agent, or the parental or sustained release formulations can comprise a therapeutically effective amount of at least one pyruvate compound or a pharmaceutically acceptable salt thereof, and at least one nitric oxide donor, and, optionally at least one therapeutic agent.

The compounds and compositions of the invention can be formulated as pharmaceutically

acceptable salt forms. Pharmaceutically acceptable salts include, for example, alkali metal salts and addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid and the like. Appropriate organic acids include, but are not limited to, aliphatic, cycloaliphatic, aromatic, heterocyclic, carboxylic and sulfonic classes of organic acids, such as, for example, formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, algenic, β-hydroxybutyric, cyclohexylaminosulfonic, galactaric and galacturonic acid and the like. Suitable pharmaceutically-acceptable base addition salts include, but are not limited to, metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine and the like. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with the compound.

While individual needs may vary, determination of optimal ranges for effective amounts of the compounds and/or compositions is within the skill of the art. Generally, the dosage required to provide an effective amount of the compounds and compositions, which can be adjusted by one of ordinary skill in the art, will vary depending on the age, health, physical condition, sex, diet, weight, extent of the dysfunction of the recipient, frequency of treatment and the nature and scope of the dysfunction or disease, medical condition of the patient, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound used, whether a drug delivery system is used, and whether the compound is administered as part of a drug combination.

The amount of a given nitrosated and/or nitrosylated pyruvate compound of the invention that will be effective in the treatment of a particular disorder or condition will depend on the

nature of the disorder or condition, and can be determined by standard clinical techniques, including reference to Goodman and Gilman, supra; The Physician's Desk Reference, Medical Economics Company, Inc., Oradell, N.J., 1995; and Drug Facts and Comparisons, Inc., St. Louis, MO, 1993. The precise dose to be used in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided by the physician and the patient's circumstances.

In one embodiment of the invention the nitrosated and/or nitrosylated pyruvate compound is administered as a daily dose of about 0.01 mg to about 2.0 mg/kg of body weight, preferably at a daily dose of about 0.1 to 1.5 mg/kg of body weight and even more preferably at a daily dose of about 0.3 to 1.0 mg/kg of body weight. The administration may be as a single dose or as an initial bolus followed by continuous infusion of the remaining portion of a complete dose over time.

The invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compounds and/or compositions of the invention, including, at least, one or more of the novel pyruvate compound, that is optionally nitrosated and/or nitrosylated, and/or at least one or more of the NO donors described herein. Associated with such kits can be additional therapeutic agents or compositions (e.g., aldosterone antagonists, alpha-adrenergic receptor antagonists, antidiabetic compounds, anti-hyperlipidemic drugs, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antioxidants, antithrombotic and vasodilator drugs, beta-adrenergic blockers, calcium channel blockers, diuretics, endothelin antagonists, H_2 receptor antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), potassium channel blockers, platelet reducing agents, proton pump inhibitors, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and the like, and mixtures of two or more thereof), devices for administering the compositions, and notices in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products which reflects approval by the agency of manufacture, use or sale for humans.

The disclosure of each patent, patent application and publication cited or described in the present specification is hereby incorporated by reference herein in its entirety.

Although the invention has been set forth in detail, one skilled in the art will appreciate

that numerous changes and modifications can be made to the invention, and that such changes and modifications can be made without departing from the spirit and scope of the invention.

CLAIMS

What is claimed is:

1. A nitrosated and/or nitrosylated pyruvate compound and pharmaceutically acceptable salts thereof.

ABSTRACT OF THE DISCLOSURE

The invention describes novel nitrosated and/or nitrosylated pyruvate compounds and pharmaceutically acceptable salts thereof, and novel compositions comprising at least one nitrosated and/or nitrosylated pyruvate compound, and, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and/or at least one therapeutic agent. The invention also provides novel compositions comprising at least one pyruvate compound and at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and/or at least one therapeutic agent. The invention also provides novel kits comprising at least one pyruvate compound, that is optionally nitrosated and/or nitrosylated, and, optionally, at least one nitric oxide donor and/or at least one therapeutic agent. The invention also provides methods for treating diseases resulting from oxidative stress, diabetes, reperfusion injury following ischemia, preservation of tissues, organs, organ parts and/or limbs.